THE PHYSIOLOGY
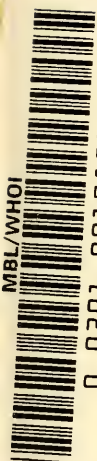# AND PHARMACOLOGY
OF THE PITUITARY BODY

BY
H. B. VAN DYKE

THE UNIVERSITY OF CHICAGO
MONOGRAPHS IN MEDICINE

THE PHYSIOLOGY AND PHARMACOLOGY
OF THE PITUITARY BODY

THE PHYSIOLOGY AND PHARMACOLOGY OF THE PITUITARY BODY

Volume II

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FOREWORD

D R. VAN DYKE has again rendered a valuable service
to biology and medicine in presenting in this second
volume his critical digest of the experimental and
clinical literature on the pituitary body that has appeared
since 1935. During these four years, while public attention
has been focused mainly on violence and war, on economic
maladjustments and social strife in many lands, and when
myopic men have clamored for a moratorium on science,
biological and medical research in some countries has still
gone on at a rate and of a quality which now calls for a second
review volume on the pituitary body alone. I think this is
clearly on the credit side of our simian ledger, even though
the pace of publication of excellent research and the making
of good scientific books bid fair to exceed our capacity for
memory and mental digestion.

The pituitary body is still the "master" among the
endocrine glands. The four additional years of research have
detracted very little from its prestige, while it has extended
its significance in several directions. A few pituitary hor-
mones have become more hypothetical than they were four
years ago, a few appear to have become more firmly estab-
lished, but, with the possible exception of the lactogenic
hormone, their chemical identity still eludes us. In fact, all
the fundamental questions anent the pituitary body, in health
and in disease, are still beyond the horizon. The role of this
gland in the normal physiology of aging has scarcely even
been formulated as a problem. The author's present winnow-
ing will help to direct the next advance on many fronts.

A. J. CARLSON

February 1939

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PREFACE

THE stream of reports on the functions and interrelationships of the pituitary body now flows at the rate of approximately 750 articles yearly. Since 1934 research has been especially active; while new and useful contributions are much less numerous than the volume of data offered would lead one to expect, nevertheless, notable advances have been made in clarifying certain aspects of the complex functions of this organ. In this respect, several fields deserve particular mention—i.e., the physiological significance of the pars neuralis, the importance of the anterior pituitary in carbohydrate metabolism, the physiology of the breasts in relation to the anterior pituitary, and the correlation of anatomical changes in the gland with alterations of function and morphology elsewhere in the body. The great interest shown in the gonadotropic hormones appears not to have led to a commensurate return. Investigation of the thyrotropic hormone probably has been least fruitful recently.

In the present volume I have undertaken to meet the need of sifting and classifying the new data and concepts and of modifying the old by endeavoring critically to review recent work on the physiology and pharmacology of the pituitary body. A brief summary of my opinion of the present state of our knowledge has been added to each chapter. The first volume included part of the reports of 1935; the present volume is believed to include references to all important experimental work published during the remainder of 1935 and during the years 1936 and 1937. In addition, some reports of 1938 are reviewed. The Bibliography (1,418 titles) represents 78 per cent of the articles which were considered.

I wish here to record my thanks to a number of colleagues who have given me the benefit of expert and critical advice.

PREFACE

Dr. R. O. Greep kindly assembled for me the information which appears in the Appendix. I am grateful to the authors and publishers—American, British, French, and German—who gave me permission to reproduce illustrations and tables. These all receive acknowledgment where the material appears.

H. B. van Dyke

New Brunswick, New Jersey
February 1939

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CHAPTER I

THE ANATOMY OF THE PITUITARY BODY

IN RECENT years the majority of the reports concerned
with the anatomy of the pituitary body have dealt with
its physiological aspects. The pituitary's largest and
most important division—the pars glandularis—has received
the greatest attention. Unfortunately the quality of the work
published varies greatly, so that many of the findings scarcely
deserve mention and serve only further to confuse any pres-
entation which attempts completeness. To a varying extent,
of course, the same remark is true of other pituitary investi-
gations which are non-morphological.

The recent additions to our knowledge of the embryology
of the pituitary body are few. The morphological and func-
tional development of the pars buccalis in larvae of anuran
amphibia (*Rana pipiens*, *R. sylvatica*) can take place without
contact with nervous tissue contrary to the views of some
embryologists (Atwell, 1937). This statement may not be
true so far as the pars tuberalis is concerned. On the other
hand, Atwell's experiments with larvae of a salamander
(*Amblystoma punctatum*) suggested that similar development
of the pars buccalis in this animal requires the presence of
nervous tissue near by. Schliefer (1935) studied the develop-
ment of the pituitary of the toad (*Bufo vulgaris*), especially as
it is related to metamorphosis. He found that development
is not complete until toward the end of metamorphosis. Also
he stated that the administration of pars neuralis extract
("hypophysin-feeding") is associated with some retardation
of metamorphosis, an increased rate of growth, and altera-
tions in the cells and pigment of the pars intermedia; it
appears fruitless to attempt to interpret these observations.
Tilney (1936) has recently made a detailed study of the de-

velopment of the human pituitary which, he emphasizes, follows a typical mammalian pattern such as that of the cat. According to Tilney, the pars glandularis (which he terms the pars distalis) develops as a medullary core almost entirely surrounded by a cortical envelope; he believed that the functional anatomy of these developmental divisions should be carefully investigated.

There have appeared recently several contributions to the comparative anatomy of the pituitary body, particularly in fishes and amphibia. Among the fishes studied were several species of skates (*Raia maculata*, *R. clavata*, and *R. brachyura* [Howes, 1936]), various selachians (Ranzi, 1937), and a number of species of bony fishes (particularly *Silurus glanis* [Lange, 1936]), including the eel, *Anguilla vulgaris* (Hagen, 1936). Some of the studies embraced physiological correlations. For example, Lange described the yearly cyclic changes in the pituitary of *S. glanis*. Ranzi found that by the histological appearance of the pars glandularis and pars intermedia it was possible to decide whether the pituitary had been removed from an immature, a normal adult, or a pregnant selachian. Hagen pointed out that the pars glandularis of the eel is largely made up of oxyphils. The volume and vascularity of the pituitary markedly increases during metamorphosis. Sato (1935) studied several anuran amphibia. Among studies in birds that of Schildmacher (1937) is best mentioned here. He investigated the histology of the pituitary in the blackbird (*Turdus merula*) in males and females at times of annual flights (spring and autumn).

THE BLOOD VESSELS OF THE PITUITARY BODY

Wislocki and King (1936) have made an important contribution to our knowledge of the vascular connections of the pituitary body and adjacent tuber cinereum. Their results indicate that the description of Popa and Fielding, especially of the hypophysio-portal system, requires extensive modification. The pars glandularis is furnished with blood by two

routes: afferent arteries and afferent portal veins which origi-
nate in the region of the stalk from a plexus both surrounding
and penetrating the infundibular stem (see Fig. 1). The ter-
minal parts of these arteries and veins unite to form the
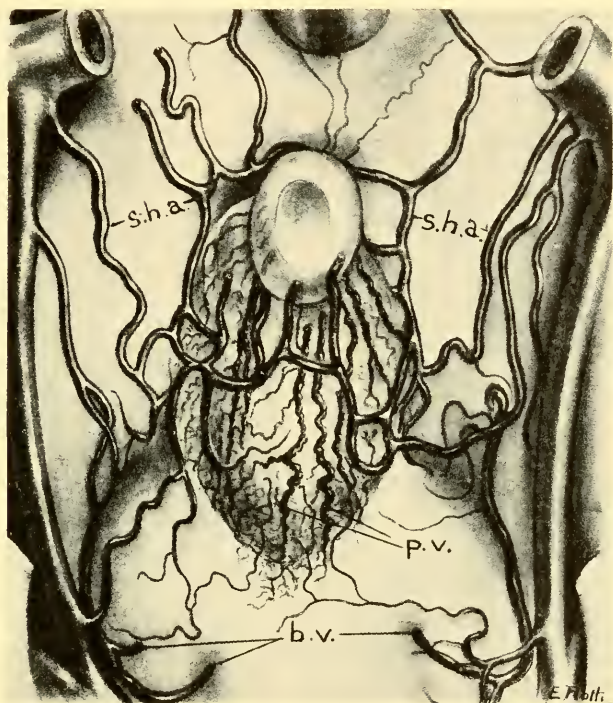
FIG. 1.—The blood vessels of the human pituitary body as revealed by a dissec-
tion of the base of the brain. *s.h.a.:* superior hypophysial arteries, anastomosing
arteries supplying the pars neuralis, pars intermedia, and pars glandularis. *p.v.:*
portal veins on the stalk. *b.v.:* basilar veins, into which blood only from the floor
of the hypothalamus flows. (From Wislocki and King, Amer. J. Anat., **58**, 421–72
[1936].)

sinusoids characteristic of the pars glandularis. Blood leaves
the pars glandularis in veins passing from the lateral poles of
the anterior lobe to the cavernous sinuses. The eminentia
saccularis, infundibulum (pars neuralis), and pars intermedia
are supplied with arteries and drained by veins which are

almost independent of those of the anterior lobe. These vessels enter and leave by the posterior pole of the pars neuralis. Contrary to Popa and Fielding, as well as many other investigators, the authors concluded that the hypophysio-portal veins receive no blood from the anterior or posterior lobes and that the hypothalamus in a vascular sense is independent of the pituitary body. On the other hand, the terminal basal portion of the tuber cinereum—the eminentia saccularis—appears from its vascular supply as well as from the readiness with which it takes up vital dyes to be one part of a unit composed of the eminentia saccularis, the stalk, and the pars neuralis. In respect of their avidity for vital dyes and their unusually rich and complex blood supply, the supraoptic region of the diencephalon and the area postrema of the "hindbrain" also appear to be tissues similar to those of the unit just described.

It is emphasized by Wislocki and King that the foregoing description is particularly true of the monkey (and probably human)[1] pituitary and hypothalamus. It should again be emphasized that their results indicate that blood flows from the hypophysio-portal vessels to the pars glandularis and not in the reverse direction, as was the contention of Popa and Fielding as well as others. The description of Wislocki and King, moreover, denies the assumption of many authors that secretions of the pituitary body have ready access to and specifically affect hypothalamic "vegetative centers."

The blood vessels of the diencephalic-hypophysial region in the cat are, in most respects, like those in the monkey; however, the eminentia saccularis is less well vascularized in the cat (Wislocki, 1937). In the cat, also, Stevens (1937) measured the total lengths and average diameters of the capillaries per unit volume of tissue of the various parts of the pituitary body. She concluded that the pars tuberalis is supplied with sinusoids even more richly than the pars glandularis. The latter was found to have a vascular bed about

[1] See also the report of Wislocki (1937).

six times as large as that of the pars neuralis which, in this respect, resembled the motor nucleus of the seventh nerve. The pars intermedia contained the smallest number of capillaries.

THE MENINGES OF THE PITUITARY BODY

New studies of the meningeal relations of the pituitary body in the dog (Schwartz, 1936) and in a number of mam-
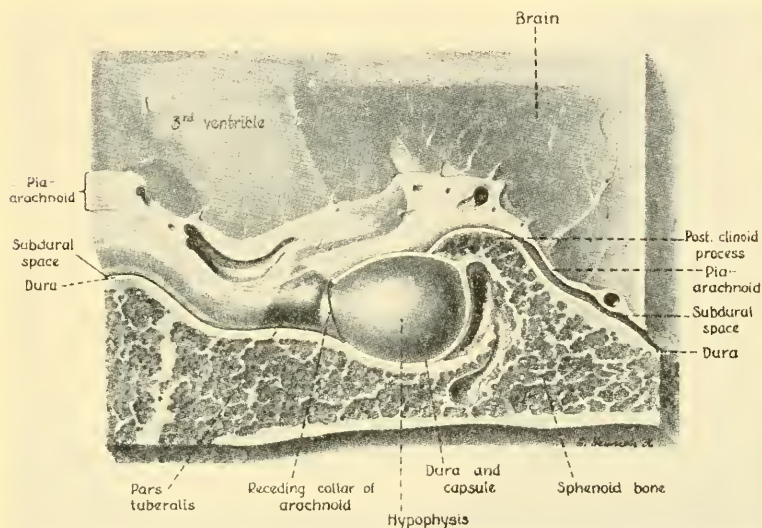
Fig. 2.—The relation of the meninges to the pituitary body of the dog. Note that the pia-arachnoid surrounds the stalk and pars tuberalis but not the remainder of the pituitary body. (From Schwartz, Anat. Rec., **67,** 35–44 [1936].)

mals, including man and the human embryo (Wislocki, 1937), have been reported. The subarachnoid space encircles the infundibular stalk but does not surround the pituitary body proper, although it may penetrate into the sella turcica a short distance in the cat and dog (see Fig. 2). The dura mater extends throughout the sella turcica and constitutes one layer of a fused structure consisting of periosteum, intrasellar dura, and pituitary capsule. Therefore there is no subdural space.

[5]

THE INNERVATION OF THE PITUITARY BODY

It has been known for many years that the pars glandularis receives sympathetic nerve fibers from the carotid plexus. In the cat these non-myelinated fibers accompany the arteries and terminate chiefly in the pars glandularis and the pars neuralis. Not all the nerve fibers degenerate after cervical sympathectomy, and some may be parasympathetic in origin (Hair, 1938). The functional significance of this innervation, however, has not yet been adequately explored. Evidence of a nervous regulation of the pars glandularis is slowly accumulating.[2] Concerning the pathways involved, however, little is known. The physiological importance of the nerve supply of the pars intermedia has been clearly suggested by experiments in amphibia and certain other cold-blooded animals. Here again, however, not much is known about the location of the innervating (efferent) neurones, although Hair found that some fibers of the supraoptico-hypophysial tract can be traced to the pars intermedia in the cat. Our best information deals with the nerve supply of the pars neuralis. Especially in recent studies employing physiological and morphological technics it has been possible to demonstrate the great dependence of the pars neuralis on certain hypothalamic nuclei, particularly the paired supraoptic nuclei. Necessarily, then, the greater part of the discussion will be concerned with the pars neuralis. Much of the review of the physiological experiments, together with an additional diagram of the nervous connections between the hypothalamus and the pars neuralis, will be found in chapter x.

The diagram reproduced as Figure 3 represents the opinion of Roussy and Mosinger on the innervation of the pituitary

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[2] Such as the effect of light on the secretion of gonadotropic hormone in birds and in one mammal, the ferret. Strong, diffuse electrical stimulation causes the liberation of gonadotropic hormone (ovulation) in the rabbit. See also the report of Collin and Hennequin (1936) on changes in the pars glandularis of the rabbit following bilateral extirpation of the superior cervical ganglia (see also chap. iii).

body. Some of the interconnections depicted represent pos-
sibilities rather than probabilities inferred from correlated
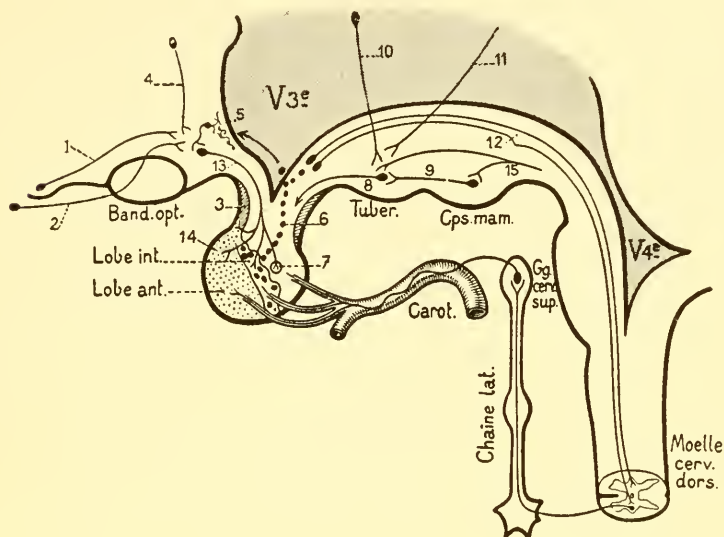
Fig. 3.—The innervation of the pituitary body according to Roussy and Mo-
singer. (From Presse méd., **44**, 1521–23 [1936].)

Band. opt.: optic tract; *Carot.*: carotid artery; *Chaîne lat.*: cervical sympa-
thetic; *Cps. mam.*: mammillary body; *Gg. cerv. sup.*: superior cervical ganglion;
Lobe ant.: pars glandularis; *Lobe int.*: pars intermedia; *Moelle cerv.-dors.*: cervico-
thoracic portion of spinal cord; $V3^e$: third ventricle; $V4^e$: fourth ventricle; *Tuber:*
tuber cinereum.

1, Amygdalo-tangential* tract (olfactory-pituitary reflexes). *2*, Retino-tan-
gential* tract (optico-pituitary reflexes). *3*, Pars tuberalis. *4*, Pathway by which
pituitary can be influenced by corpus striatum and globus pallidus. *5*, Subependy-
mal network of sensory nerves. *6*, "Neurocrinie hypophyso-hypothalamique." *7*,
Islet of glandular cells in pars neuralis. *8*, Tubero-hypophysial tract. *9*, Mammillo-
hypothalamic tract. *10*, Thalamo-hypothalamic pathways. *11*, Cortico-hypothal-
amic pathways. *12*, Decussation of descending hypothalamic pathways. *13*, Hypo-
thalamico-hypophysial tract. *14*, Zone of transition. *15*, Central sensory pathways.

* Tangential or supraoptic nucleus.

morphological-physiological experiments. An example of
a diagram based upon such experiments is that of Figure 4.

The function and, indeed, the morphological maintenance
of the pars neuralis depends upon the normal flow of im-

[7]

pulses from certain nuclei in the hypothalamus to the neural
lobe. (The most complete experiments have been performed
in cats by Fisher, Ingram, and Ranson.) The important nu-
clei are the paired supraoptic nuclei which supply most of the
nerve fibers of the pars neuralis as well as a few fibers to the
different divisions of the pars buccalis. Both of the nuclei
must be destroyed or cut off from the pars neuralis before the
latter undergoes atrophy and ceases to elaborate its hor-
mones. The neurones of the supraoptic nuclei degenerate and
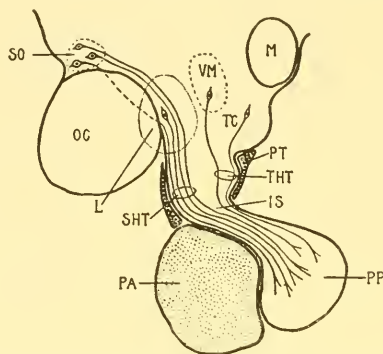
FIG. 4.—Diagram of hypothalamico-hypophysial fiber system of the monkey.
(From Ingram, Fisher, and Ranson, Arch. intern. Med., **57,** 1067–80 [1936].) Diabe-
tes insipidus can be produced by lesions in the circumscribed region *L. IS:* stalk;
M: mammillary body; *OC:* optic chiasm; *PA:* pars glandularis; *PP:* pars neuralis;
PT: pars tuberalis; *SHT:* supraoptico-hypophysial tract; *SO:* supraoptic nucleus;
VM: ventromedial component of supraoptic nucleus; *TC:* tuber cinereum; *THT:*
tubero-hypophysial tract. As indicated by a broken line, it is possible that fibers
of the supraoptico-hypophysial tract pass through the optic chiasm.

disappear after hypophysectomy—i.e., in the dog or rat
(Hare, 1937; Rasmussen, 1937) or after interruption of the
supraoptico-hypophysial tract. The filiform or paraventricu-
lar nuclei perhaps also directly or indirectly—i.e., by way of
interposed synapses with neurones of other nuclei—innervate
the pars neuralis. The morphological evidence for this inter-
pretation is, however, better than the neurological.[3]

[3] The following are recently published references to authors who have made ob-
servations on other parts of the pituitary and its possible central connections: Col-
lin (1935), Collin and Fontaine (1936), Collin and Hennequin (1936), and Roussy
and Mosinger (1935–36).

Hair (1938) described knoblike enlargements projecting from nerves distributed in the pars glandularis, pars intermedia, and pars tuberalis of the cat's pituitary body. These enlargements lay in contact with the epithelial cells. In the pars neuralis the nerves terminated in bulblike structures similar to those described by others in the neural lobe of the ox and of man.
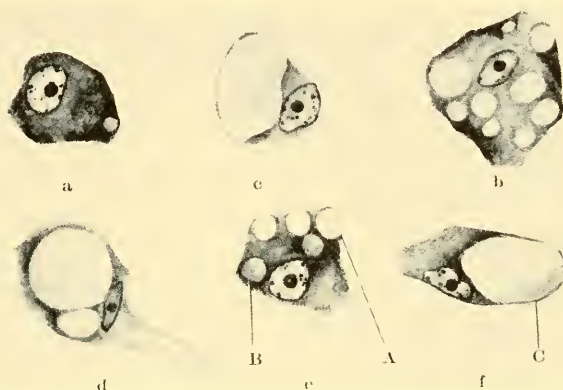
FIG. 5.—Colloid-formation in neurones of the supraoptic and paraventricular nuclei. (From Peters, Z. Neur., **154**, 331–44 [1936].) Colloid *a* as fine droplets, *b* diffusely distributed, and *c* and *d* as large accumulations believed to follow coalescence of smaller droplets. Vacuoles may appear to be empty, *A* of *e*, or partly filled, *C* of *f*, or completely filled, *B* of *e*, with colloid.

A number of French and German authors[4] have called attention to the peculiar morphology of the neurones of certain hypothalamic centers. Some of the morphological variations which may occur in the cells of the supraoptic and paraventricular nuclei are illustrated in Figure 5. The formation of colloid by these or homologous neurones is said to be recognizable not only in man and other mammals but also in other vertebrates such as reptiles, amphibia, and fishes, as well as in

[4] Collin and collaborators (see the earlier volume), Scharrer (1933–35), Gaupp (1935), Gaupp and Scharrer (1935), Peters (1935), and Roussy and Mosinger (1935–36). Florentin (1937) discusses changes related to secretory activity of the pars intermedia (toad). Roussy and Mosinger (1937) also review anatomical evidence for the secretion of pituitary hormones into the cerebrospinal fluid.

one invertebrate, the snail. Other morphological characteristics which have been described in these nuclei are multinuclear cells, endocellular capillaries, and degeneration and disintegration of the cells. All these observations seem to place the neurones of the supraoptic and paraventricular (and perhaps the tubero-mammillary) nuclei in a category different from that of other cells of the central nervous system, although Peters found colloid inclusions in cells of certain nuclei of the medulla oblongata.

The evidence that such cells secrete colloid and are to be considered a "diencephalic gland" is morphological and does not deserve acceptance at this time. The "secretory activity" of these cells appears to be slight in childhood; it is not otherwise correlated with age and is not altered as a result of nervous or endocrine diseases.

THE PARS INTERMEDIA, THE PARS NEURALIS AND THE PARS TUBERALIS

It has again been emphasized that the pars intermedia of man and the anthropoid apes is a structure so rudimentary in appearance that it appears to have no important function (Berblinger and Burgdorf, 1935; Plaut, 1936; and Scriba, 1936). Frequently, also, the human pituitary contains no residual cleft of Rathke's pouch. In the pituitary of the porpoise[5] and the whale,[6] the pars glandularis is completely separated from the pars neuralis by a leptomeningeal-dural fold. The embryologic development of the organ in the porpoise and whale is therefore apparently different from that in other mammals. No pars intermedia can be recognized in the cetacean pituitary.[7] According to Benjamin (1935), the deposits of pigment in the pars intermedia and in the pars tuberalis of wild and hooded rats—but not present in pure

[5] *Tursiops truncatus.*

[6] *Balaenoptera physalus, B. sibbaldi,* and *Physeter megalocephalus* (see Geiling, 1935; and Wislocki and Geiling, 1936).

[7] Whether or not a pars intermedia can be identified in the bird's pituitary is still undecided (see the discussion of Wislocki and Geiling).

albinos—originates in the leptomeninges and, after development, is found in the connective-tissue septa.

The cells of the pars intermedia secrete the chromatosome-dispersing hormone. If, however, the pars intermedia is rudimentary and perhaps non-functional (man) or absent (fowl? cetacean), the hormone is still formed by cells of the pars glandularis.

The basophilic cells of the pars neuralis have been carefully studied by numerous authors because of their possible relationship to clinical disorders such as hypertension—a view particularly emphasized by Cushing. These cells are probably derived from the pars intermedia (Andreis, 1935; and Rasmussen, 1936) and, it is generally agreed, increase in numbers particularly after middle age, when, of course, essential hypertension is more frequently present. However, it appears clear that there is no convincing correlation between the development or presence of hypertension and the ingrowth (and hyperplasia) of basophilic cells in the pars neuralis. The association of hypertension and this morphological change is fortuitous (Marcano, 1935; Hawking, 1936; Rasmussen, 1936; and Scriba, 1936). Likewise these basophilic cells probably have nothing to do with the elaboration of the oxytocic and pressor–diuresis-inhibiting hormones of the pars neuralis. The cetacean pars neuralis is entirely separated from the pars buccalis by meninges and yet contains the characteristic pars neuralis hormones (Geiling, 1935). In the cat, after sufficient injury of the supraoptico-hypophysial nervous connections, the amount of oxytocic and pressor hormones in the pars neuralis is markedly reduced in association with atrophy of the pars neuralis; yet there is little change in the pars intermedia (Fisher and Ingram).

The hyaline bodies of Herring, which can be found in the pars neuralis of the whale (Wislocki and Geiling, 1936), are therefore not derived from juxtaposed cells of the pars buccalis (pars intermedia) as has been suggested from studies of the pituitary of other mammals. In fact, Gersh and Tarr

(1935) offer good evidence that such hyaline bodies are fixation artefacts and are unrelated to the amount of pressor hormone in the pars neuralis. Gersh and Tarr studied the pars neuralis of six mammals and of the fowl. True secretory cells have long been sought in the pars neuralis. Recently Gersh (1937) described parenchymatous "glandular" cells more or less uniformly distributed in the pars neuralis and containing granules or lipoid droplets. They could be identified in the neural lobe of nearly all mammals and of two birds (fowl and pigeon). They appear to be supplied with nerve fibers passing down the stalk and probably secrete the diuresis-inhibiting (vasopressor) hormone. They were found to undergo degeneration after section of the stalk and to increase in number and size if water was withheld. The brown and black pigment of the human pars neuralis has been studied recently by Roussy and Mosinger (1935). Trossarelli (1935) investigated the connective tissue and nerve fibers of the pars neuralis. He confirmed Tello's earlier description of the club-shape of some of the nerve endings of the pars neuralis. Although true nerve cells heretofore have not been identified in the pars neuralis, Kasahara (1935) stated that nerve cells with growing fibers could be found in his cultures of pars neuralis tissue obtained from young rabbits. The distribution of mast cells in the infundibulum and pars neuralis of the ox, the cat, and man has been studied by Gray (1935). The mast cells often appeared to be closely associated with the primary capillary network of the hypophysio-portal system.

There have been no important additions to our knowledge of the morphology of the pars tuberalis. Its functional importance is still unknown, although Biggart believed that it secretes the diuresis-inhibiting hormone.

THE PARS GLANDULARIS

As has already been mentioned, the majority of the recent reports dealing with the anatomy of the pituitary body are chiefly concerned with the physiological anatomy of the pars

glandularis. In addition, there are a few miscellaneous reports which will be considered at the end of this section. Some of the most interesting interpretations are the result of studies of human pituitaries. Furthermore, confidence in the validity of the conclusions reached is possible because, in the best of these reports, actual cell-counts rather than impressions were used in gathering data. Likewise, in a number of reports of an experimental nature this technic has been used. Finally, it is unfortunately also true that morphological investigations of the pars glandularis—whether of man or of animals—in which conclusions of a quantitative character are reached without any recognition of the necessity of founding these on a technic quantitatively sound are often the principal means of confusing efforts to make a modest start in satisfactorily picturing the function(s) of the cells of the anterior pituitary.

There still is no agreement in reference to the relationship between the reserve cells and the chromophil cells.[8] Franck, in several reports published in 1935–37, concluded, as many authors have before him, that the chromophil cells are derived from the reserve cells. He believed that there exist several varieties of oxyphils and basophils, and that the latter in turn are derived from oxyphils. Kirkman (1937), like Franck, also used the guinea pig. Kirkman's elaborate study included a careful analysis of previous reports and should be read by those particularly interested in the physiological anatomy of the pars glandularis. He studied the anterior pituitary of guinea pigs during the oestrous cycle, in pregnancy, postpartum, after gonadectomy, in fetal life, etc. Figure 6 is reproduced from a report by Severinghaus and indicates, in diagrammatic form, some views which have been held as to the relationship between the reserve cells (chromophobes) and the chromophils (oxyphils or acidophils and basophils). This author (1937) has recently reviewed the relationship of

[8] The report of Collin and Stutinsky (1937) contains a description of cellular peculiarities of the anterior pituitary of the frog.
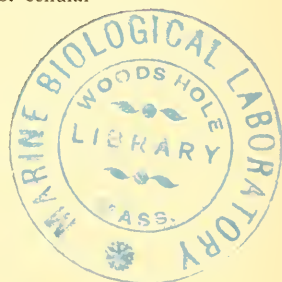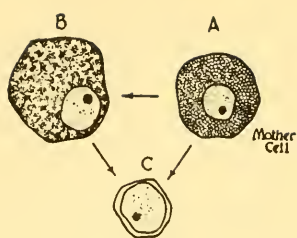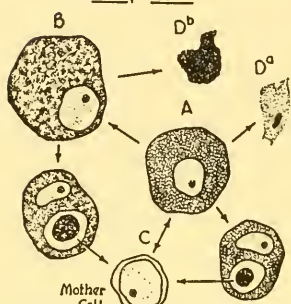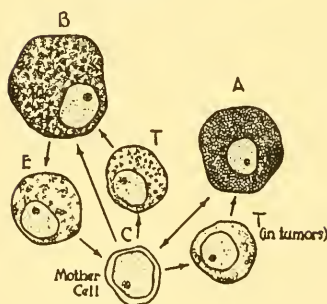
A · ACIDOPHILE   Dᵃ, Dᵇ, Dᶜ · DEGENERATING CELLS

B · BASOPHILE   E · CELL SHOWING GRANULAR ELIMINATION
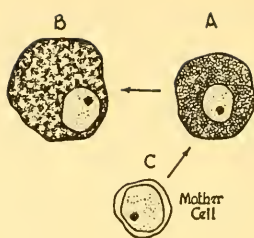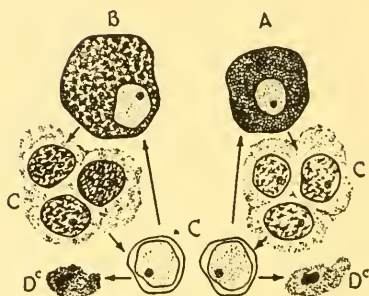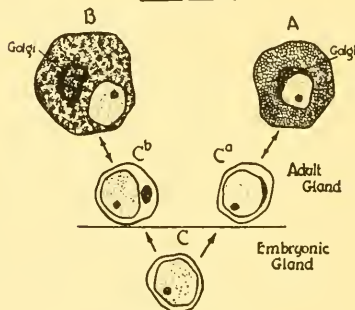
C · CHROMOPHOBE   T · TRANSITIONAL (ÜBERGANGZELL)

Cᵃ, Cᵇ · ACIDOPHILIC AND BASOPHILIC CHROMOPHOBES RESPECTIVELY

FIG. 6.—Diagrams illustrating views of different authors on the relationships of cells of the pars glandularis. (From Severinghaus, Physiol. Rev., **17,** 556–88 [1937].)
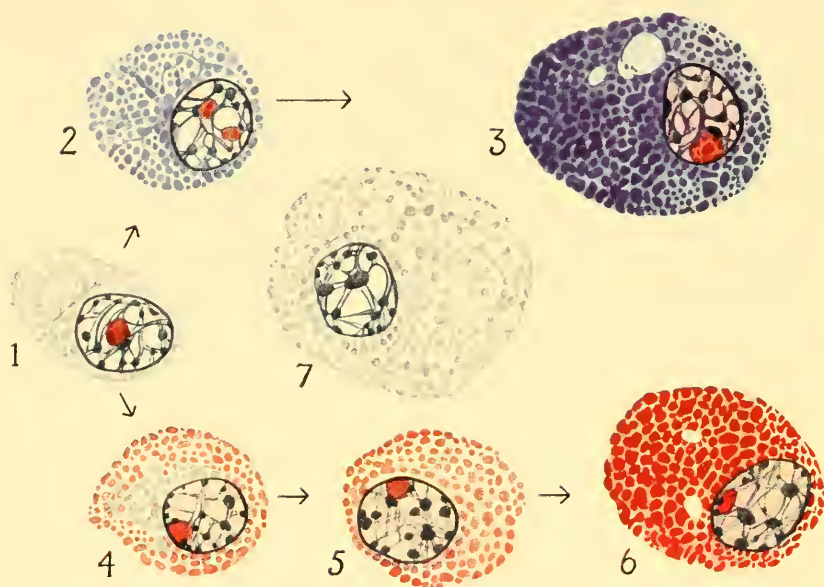
FIG. 7.—Diagram of the relationship of the cells of the pars glandularis. (From Crooke and Russell, J. Path. Bact., 40, 255–83 [1935].) Staining by authors' differential method. *1*, Reserve cell. *2*, Transitional basophil. *3*, "Adult" basophil. *4* and *5*, Oxyphils in early and later transition. *6*, "Adult" oxyphil. *7*, Exceptionally large reserve cell.

the cellular morphology of the pars glandularis to the gland's physiological activity. The view of Crooke and Russell (1935) as to the cellular relationships in the human anterior pituitary is illustrated in Figure 7.

Dawson (1937) has named a specialized portion of the pars glandularis the "zona tuberalis" because of its location. In the cat and rabbit this part of the anterior pituitary consists largely of reserve cells and basophils, the proportions of which vary greatly in response to changes in the reproductive cycle, gonadectomy, adrenalectomy, etc.

According to Sanchez-Calvo (1937), if guinea pigs or rabbits are kept in a dark room, there occurs, among other changes, a marked increase in the proportion of oxyphils in the anterior pituitary. The maximum change was observed after the animals had been kept for 72 hours in darkness.

The relationship between the reproductive organs or their internal secretions and the anatomy of the pars glandularis.—The relationship between normal sexual activity and the morphology of the pars glandularis recently has been studied in the frog (Zahl, 1935) and pigeon (Mârza and Blinov, 1936). Zahl concluded that the important changes which can be correlated with the annual sexual cycle of several species of *Rana* involve the oxyphil and reserve cells. (The small basophils appeared to be unimportant.) During the winter months the number of oxyphils containing "fuchsinophil" droplets[9] increases at the expense of the reserve cells and reaches its peak in the spring. Following the breeding season, the number of oxyphils undergoes a gradual reduction and is lowest in the late summer and autumn. According to Mârza and Blinov, the pituitary of the female pigeon enlarges at about the time of ovulation without, however, any apparent change in the number of reserve or basophil cells. Their technic did not permit them to draw any conclusions concerning the oxyphils.

Opinions on the histological appearance of the pars glandu-

[9] Zahl also speaks of fuchsinophil droplets in cells "otherwise chromophobic."

laris of mammals like the rat at different stages of the oestrous cycle vary greatly. The recent careful study of Wolfe (1935), who used both qualitative and quantitative technics, led him to conclude that in the female rat the proportion of none of the cells—disregarding finer qualitative details such as the content of granules—varies at different stages of the oestrous cycle.[10] He believed that the only clearcut cyclic change is in the granules of the basophils. These granules are most numerous in pro-oestrus and rapidly diminish in number during oestrus and metoestrus. Pfeiffer (1937) supplemented his other experiments designed to alter the sexual characteristics of pituitary function in rats (see chap. iii) by anatomical studies. The distribution of cells typical of the male or female pituitary could be produced by transplanting testes into spayed females or ovaries into castrated males. The anterior pituitary of animals with both ovarian and testicular grafts tended to be of the male type. After puberty and, therefore, after sexual differentiation of the pars glandularis, the distribution of cells could not be altered.

The alterations in the pituitary accompanying parturition and the onset of lactation have interested several investigators. Collin and Florentin (1935) who used guinea pigs, as well as Weis (1935) who used rats, stated that an unusual and marked predominance of reserve cells is observed at parturition and for about 24 hours later. They believed that this change is related to the initiation of lactation. Collin and Florentin also concluded that the oxyphil is the more numerous chromophil during the first half of pregnancy, whereas the basophil predominates toward the end of pregnancy. Desclin (1936) was interested in the significance of the corpus luteum in maintaining the pituitary's lactation morphology in the rat. He found that the latter persists after ovariectomy, provided that the young continue to suckle. If, how-

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[10] The proportions of the different cells confirmed Wolfe's previous report. The means and standard deviations were: basophils, 4.1 ± 1.3 per cent; oxyphils, 34.2 ± 4.3 per cent; reserve cells, 61.8 ± 4.4 per cent.

ever, the young are removed, the pars glandularis assumes the appearance characteristic of gonadectomized animals (increased numbers of basophils, "castration-cells"). Kraus (1935) has advanced the opinion that the "pregnancy-cells" of the pars glandularis, growing initially because of placental stimulation, secrete the lactogenic hormone which is released into the circulation after the expulsion of the placenta. He believed that suckling is the stimulus responsible for the continued secretion of the lactogenic hormone by these cells.

Characteristic changes in the anterior pituitary following gonadectomy can be consistently observed in the rat and have already been described in the former volume. These changes chiefly involve the basophils which increase in number and later hypertrophy and become vacuolated. Such basophils containing a single large vacuole have been named castration-cells. In other animals, such as the guinea pig, contradictory descriptions of the changes in the pars glandularis following gonadectomy continue to appear. Unlike Severinghaus, Nelson (1935) declared that gonadectomy (or cryptorchidism) is followed by a slight but definite increase in the percentage of basophils in the guinea pig's anterior pituitary; however, Nelson agrees that castration-cells of the murine type are rare. An increased amount of colloid has been described in other studies of the pituitary of gonadectomized animals. Nelson mentions that thyroid-like follicles containing colloid are prominent in the anterior pituitary of gonadectomized or cryptorchid guinea pigs. Tuchmann (1937), who also studied the pituitary of gonadectomized guinea pigs, observed an entirely different change—i.e., a progressive, marked increase in the proportion of oxyphils. Both Nelson and Tuchmann were able to reverse the changes caused by gonadectomy by injecting oestrin. The reader is referred to the earlier volume for a description of anterior pituitary changes attributed to gonadectomy or injury of the gonads in man and other mammals.

The other recent reports deal with the correction or re-

versal of castration changes in the pituitary of the rat.[11] It is well known that several oestrogens and androgens cause reversal of the changes, so that the pituitary may assume a normal appearance both grossly and microscopically. Hohlweg (1935) insisted that progesterone alone (0.54 mg. daily for 15 days to adult or immature spayed rats) does not alter the changes in the pituitary due to gonadectomy. The results of Migliavacca (1936) agreed with those of Hohlweg. Therefore the findings of Clauberg and Breipohl to the contrary lack confirmation. Nelson and Gallagher (1935–36), in agreement with others, found that male hormone whether from urine or testis prevents castration changes in the rat's pituitary. Similar effects with two pure androgens, androstane diol and androstene dione, were also described.[12] Carcinogenic substances (benzpyrene and a dibenzanthracene diol)[13] can prevent the pituitary changes due to gonadectomy (Wolfe, 1936; and Tuchmann, 1937).

The effects of oestrogenic and androgenic substances on the pars glandularis are, of course, not limited to the correction of gonadectomy changes. In the past few years several authors have reported on the changes appearing in the pituitary of normal animals, both immature and adult (mouse, rat, guinea pig, and rabbit), particularly after the injection of oestradiol benzoate or oestrone.[14] The alterations about to be described vary, depending upon dosage, preparation used, duration of injections, sex, age, etc. The variations for the purpose of this review, however, are not sufficiently impor-

[11] The relative importance of the interstitial cells and the germinal epithelium in preventing "castration" changes in the pituitary remains undecided. De Fremery (1936) minimizes the importance of the "sex hormones."

[12] Other experiments with androgens have been reported by Allanson, Hohlweg, Wolfe and Hamilton, and Yanagita.

[13] See also the report of Tuchmann and Demay (1936).

[14] 1935: Nelson, Wolfe, Wolfe and Phelps; 1936: Halpern and D'Amour, Wolfe, Wolfe and Chadwick; 1937: Wolfe. It appears that luteinization of the ovaries is definitely associated with the pituitary changes in female rats. Martins (1936) could detect an increased vascularity of the pituitary, transplanted to the anterior chamber of the eye, 24–48 hours after the injection of a large dose of oestradiol benzoate.

tant to justify a detailed description. Often the dose of the oestrogen has been large (e.g., 200 rat-units of oestradiol benzoate daily for 10 days), so that the effects may be such a distortion of the physiological as to be chiefly of pharmacological importance. The first and most important change is a loss of granules from the basophils; in addition, the percentage of basophils is reduced. Especially after large doses, a similar loss of granules occurs in the oxyphils. Owing to hypertrophy of the anterior pituitary, the proportion, but probably not the number, of these cells diminishes. Several of the authors concluded that "degranulated" basophils are transformed into reserve cells. Such a transformation only in a small part accounts for a simultaneous marked increase in the percentage and total number of the reserve cells in which numerous mitoses can often be observed. The hypertrophy of the pars glandularis is due to the hyperplasia of reserve cells.[15]

Usually the injection of a large dose of an oestrogen produces a considerable hypertrophy of the anterior pituitary (2–3 times normal size). Enormous doses of an oestrogen may correspondingly accentuate the change, so that the hyperplasia of the reserve cells is indistinguishable from a neoplasm (reserve-cell adenoma). A change of this sort was first produced by Cramer and Horning (1936) in mice (see Fig. 8). The authors were primarily interested in the production of mammary carcinoma by the application of a solution of oestrone (0.01 per cent dissolved in chloroform) to the skin, through which the hormone was readily absorbed. In several mice with large hemorrhagic adenomata composed almost entirely of reserve cells, there were cachexia and degenerative changes in the adrenal cortex, in addition to the expected regressive alterations in the gonads. The authors suggested that the mice with pituitary adenomata were suffering from

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[15] The response of the transplanted pituitary is similar; so it is not likely that the effects depend to an important extent on the nervous system, as some authors have asserted (Desclin and Grégoire, 1936).

a marked hypophysial deficiency, probably because of the disappearance of the chromophilic cells. Confirmatory experiments in rats have been reported by McEuen, Selye, and
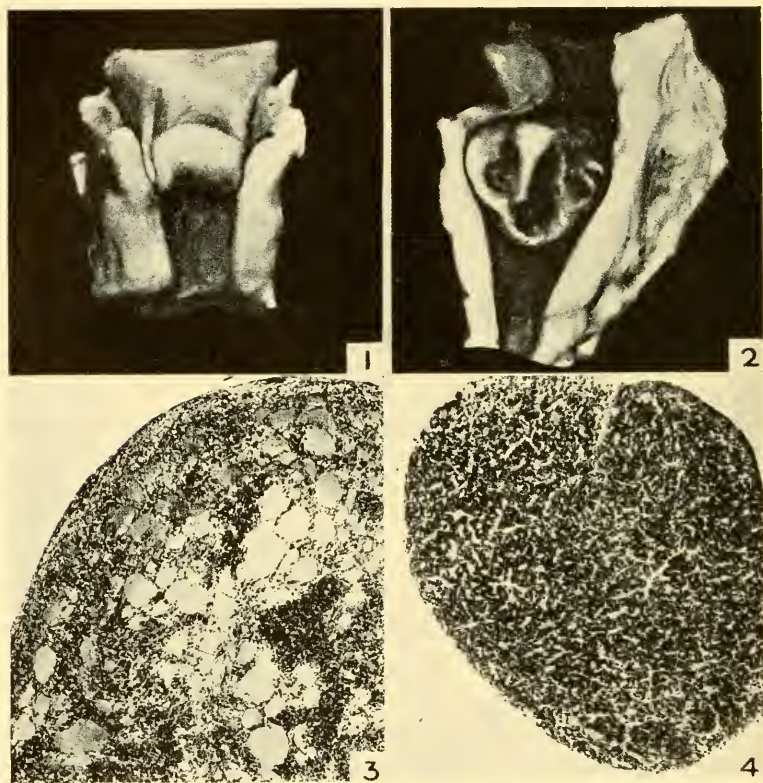
Fig. 8.—The action of large doses of oestrone, administered over a period of 6 months, on the pituitary of the mouse. (From Cramer and Horning, Lancet, 230, 247–49 [1936].) *1*, Gross appearance of normal pituitary and optic nerves. *2*, Pituitary of treated male mouse illustrating marked congestion of the pars glandularis and compression of optic nerve. *3*, Photomicrograph of pars glandularis of treated mouse (*2*) showing large hemorrhagic areas. *4*, Photomicrograph of glandularis of normal mouse at a slightly higher magnification than *3*.

Collip (1936) and by Zondek (1936). It has not been convincingly shown—as Zondek believed—that such pituitary adenomata are produced much more readily in male than in female rats. Lacassagne and Nyka (1937) concluded that the

effect of an oestrogen on the pituitary varies in different strains of mice.

Selye, Browne, and Collip (1936) injected 4 mg. of progesterone into young, mature female rats for 12 days. This treatment was followed by some reduction in the size of the ovaries (23 per cent) and some increase in the pituitary's weight (29 per cent). In the pars glandularis of the injected animals there was found "a great number of small cells with relatively dense chromatin."

Testosterone (or its propionate) causes no pituitary hypertrophy (McEuen, Selye, and Collip, 1937) and in this respect differs from oestradiol or oestrone. However, like the oestrogens it brings about a degranulation of the basophils (Wolfe and Hamilton, 1937).

Wolfe (1935) and Wolfe and Phelps (1935) reported that the effects of prolan on the pars glandularis of the adult rat resemble those of an oestrogen—i.e., loss of granules from basophils (and oxyphils) and hyperplasia of reserve cells. Apparently these changes are due to the liberation of oestrogen or androgen from the gonad stimulated by prolan. In 1937 Wolfe stated that prolan prevented some of the similar effects of oestradiol in immature female rats. In comparison with the pituitary of animals given only oestradiol, that of animals receiving both prolan and oestrogen was less hypertrophied and contained more basophils which were normal in respect of granules.

The relationship between other glands of internal secretion and the anatomy of the pars glandularis. 1. *The thyroid.*—The pars glandularis of the rabbit increases about 50 per cent in weight after thyroidectomy performed 159–333 days previously (van Dyke and Chen, 1935). Franck (1936) stated that the administration of thyroid extract or thyroxin (and, to a less extent, adrenal cortical hormone) to guinea pigs causes a reduction of the number of granules in the oxyphils. The number of basophils containing granules was thought also to be reduced. Franck also stated that an extract containing thyro-

tropic and adrenotropic hormone caused similar changes. Iodine, KI, or diiodotyrosine were found to lessen the effects (Franck, 1937).

There has been some discussion as to the nature of the changes in basophils in thyroidectomized as compared with gonadectomized animals. Nelson and Hickman (1937), although affirming that they could distinguish between the alterations in basophils due to thyroidectomy or gonadectomy, contended that the same basophils are affected by either operation. They found that changes due to thyroidectomy, except degranulation, could be corrected by the administration of oestrone. Guyer and Claus (1937) believed that the formation of vacuoles in the basophils is due to accumulation of secretion after gonadectomy, whereas after thyroidectomy it is the result of cellular degeneration. Zeckwer (1937) particularly supports the view that the thyroidectomy and gonadectomy cells of the anterior pituitary are different and can be identified morphologically.

2. *The adrenals.*—Lippross (1936), using rats instead of guinea pigs, found no significant changes in the morphology of the pituitary—and adrenals and gonads—after the prolonged administration of adrenal cortical hormone or epinephrine. Therefore, his findings did not confirm those of Franck.

The compensatory hypertrophy of an adrenal gland after the extirpation of its mate depends chiefly upon the secretion of an adrenal cortical stimulating hormone by the pars glandularis. Zeckwer (1937–38), taking into account the changes occurring in both adrenals following thyroidectomy or gonadectomy, studied the effects of these operations on compensatory adrenal hypertrophy in relation to the histology of the pituitary. She concluded that the oxyphils, which tend to disappear after thyroidectomy, do not secrete the adrenotropic hormone. Also, this hormone was thought not to be secreted by the thyroidectomy-cells or castration-cells, inasmuch as the degree of compensatory hyper-

trophy could not be correlated with the number of either cell type. Therefore, she surmised that the adrenal cortical stimulating hormone is secreted by the basophils (see also pp. 15, 21–22).

The change in the morphology of the pituitary characteristic of adrenal insufficiency is a reduction, sometimes very marked, in the percentage of basophils. Grollman and Firor (1935) found that this change, accompanied by an increased vascularity of the pituitary, is very marked in the dog. In the rat the reduction of the number of basophils is less prominent; however, the staining of these cells is "very abnormal." Recently, the cells of the hypophyses from patients with severe adrenal insufficiency (Addison's disease or atrophy of adrenals) have been counted by several investigators (Crooke and Russell, 1935; Hawking, 1936). The percentage of basophils was found to be greatly reduced (e.g., 0.06–0.5 per cent compared with 7–11 per cent in a normal series).[16] A considerable number of abnormal transitional basophils was encountered in the series of Crooke and Russell. The proportion of oxyphils also was abnormally low, whereas the proportion of reserve cells was abnormally high.

3. *The pancreas.*—After repeated injections of insulin into guinea pigs, the pars glandularis is said to be composed of an increased number of oxyphils with a corresponding diminution in the number of reserve cells (Kahn, 1935). On the other hand, Gentile and Amato (1936) stated that pancreatectomy in the dog is also followed by an increase in the proportion of oxyphils which, however, appear relatively nongranular. The volume of all the cells was found to be increased. Kahn and Waledinskaja (1936) concluded that partial pancreatectomy in the rabbit is followed by degenerative changes in the oxyphils and that the magnitude of these changes depends upon the degree of pancreatic insufficiency. An investigation of the pituitary of normal cats and of cats

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[16] Confirmatory reports without cell-counts have been published by Andreis (1935) and Meesen (1935).

sacrificed at various intervals after complete pancreatectomy was made by Fichera and Ferroni (1937). The authors believed that the pituitary undergoes hypertrophy and that a marked increase in the proportion of reserve cells at the expense of the oxyphils takes place as a result of the operation.

4. *The parathyroids.*—The pituitary of male rats after parathyroidectomy or repeated injections of parathyroid hormone or a solution of $CaCl_2$ was studied by Takahisa (1936). It was his belief that the principal alteration is in the oxyphils—the proportion increasing with parathyroid deficiency and diminishing if there is an excess of parathyroid hormone in the body's circulating fluids. The administration of a solution of $CaCl_2$ appeared to cause changes resembling those of parathyroid deficiency.

5. *The thymus.*—Clark, Steinberg, and Rowntree (1936) investigated the effects of a thymus extract on the distribution of cells in the pars glandularis of the rat. Especially in very young male rats growing at a precocious rate (age: 0–13 days) the percentage of oxyphils was almost twice that in the anterior pituitary of control animals. The authors correlate this change with the rapid growth observed. In female rats of a corresponding age, however, the increase in the proportion of oxyphils was only about 25 per cent. In older rats (age: 13–45 days) no differences were found.

6. *Attempts to correlate changes in the human pituitary with alterations in other endocrine glands or with disease syndromes.*—The syndrome of Cushing, which he named pituitary basophilism, now appears not to be related to a basophil adenoma of the pars glandularis as Cushing first believed. Susman (1934) found adenomata in 8 per cent of 260 human pituitaries which he examined. Nearly half the adenomata (eight of seventeen) were basophilic; yet Cushing's syndrome was not present. On the other hand, the syndrome may be present in the absence of a basophil adenoma. Crooke (1935) made the important observation that a hyaline change in the

basophils of the anterior pituitary invariably is associated with typical pituitary basophilism[17] in the absence or presence of basophil adenoma, a neoplasm of the thymus, or a hyperplasia of the adrenal cortex. A similar hyaline change in a few cells was found in 9 of 350 hypophyses of individuals without Cushing's syndrome. Another careful investigator of the pituitary, Rasmussen (1936), has fully confirmed Crooke's observations in three additional cases. Rasmussen also agreed that such hyaline changes in the basophils are rare in other diseases such as essential hypertension, eclampsia, etc.

Hawking (1936) as well as Rasmussen (1936) have made actual counts of the various cells occurring in the pars glandularis of patients afflicted with various chronic diseases. As a result, it was concluded that no convincing change in the morphology of the pars glandularis occurs as a result of essential hypertension, diabetes mellitus, and Graves's disease. Using less exact methods, Kraus (1935)[18] and Spark (1935) came to a similar conclusion regarding hypertension and eclampsia. Müller (1936) stated that he discovered twelve adenomata of the anterior pituitary (mostly reserve-cell adenomata) in twenty cases of adiposity but only two in twenty control cases (normal or of cachexia). Apparently the excretion of gonadotropic hormone in the urine, revealed by the production of ovulation in rabbits, may or may not be associated with various neoplasms of the pars glandularis (McCullagh and Cuyler, 1937). According to Susman (1935), a diminution in the number of oxyphils is characteristic of the pituitary of patients dying largely as a result of shock. Also without making cell-counts, Meesen (1935) believed that there is some correlation between basophilic invasion of the

[17] All twelve patients from whom Crooke's material was obtained had the following symptoms: an adiposity of the face and trunk; a plethoric, florid, or dusky complexion; a persistently high blood pressure; amenorrhea or impotence (if past puberty). In nearly all there were cutaneous striae of the abdomen or thighs and glycosuria or lowered sugar tolerance. In some there was a severe osteoporosis.

[18] Kraus suggested that an apparent increase in the proportion of basophils in renal disease and other conditions, including advancing age, may be of some ill-defined compensatory nature.

pars neuralis and essential hypertension, as well as between a proliferation of the oxyphils (secreting growth-promoting hormone?) and the growth of sarcomata.

Erdheim (1936) suggested that pregnancy-cells, which clearly are not the source of prolan, secrete a hormone promoting the growth of the fetus and some of the maternal parts. He regarded the similar cells appearing in the pituitary of patients with congenital aplasia of the thyroid as the pituitary's attempt to compensate for the harmful effect of thyroid deficiency on body-growth.

The reduction in the percentage of basophils, as well as a similar but less prominent change in the oxyphils, in the pituitary of patients with Addison's disease has already been described.

Miscellaneous observations.—Andersen, Prest, and Victor (1937) investigated the metabolism of the isolated pars glandularis of the rat at different stages of sexual activity, including pregnancy and lactation. They concluded that the metabolism of the gland could not be correlated with the percentage of basophils as determined by Wolfe and his colleagues. The pars glandularis was found to be heaviest during oestrus.

Several authors have reported their impressions of the changes in the pars glandularis due to administration or deficiency of various vitamins. Giędosz (1935) stated that repeated subcutaneous injections of a solution containing vitamin A into rabbits bring about an increase in the number of oxyphils and, to a less extent, in the number of basophils. Intravenous injections of a solution of vitamin C were followed by similar changes. The pituitary of vitamin B_1 deficiency (six human cases of beriberi) was investigated by Marburg and Wenckebach (1936). The pars glandularis frequently contained necrotic areas; the oxyphils and basophils often were separated into adenoma-like groups. They suggested that apparent holocrine degeneration of the basophils of the pars neuralis might be related to the circulatory

disorders of the condition. According to Nitzescu and Bra-
tiano (1936), changes in the oxyphils follow the administra-
tion of enormous doses of vitamin D to the dog. Stein (1935)
reviewed the literature dealing with alterations in the pitui-
tary as a result of a deficiency of vitamin E. He himself could
find no difference in the size or weight of the various lobes or
in the percentage of different cells by comparing the hypoph-
yses of female rats cured of a vitamin-E deficiency with
those of rats on a vitamin-E deficient diet. Confirmatory re-
sults were obtained by Müller and Müller (1937). However,
in three male rats (on a diet free from vitamin E for 280 days)
the authors found moderate castration changes in the ante-
rior pituitary.

The pituitary has been successfully transplanted into the
anterior chamber of the eyes of rabbits and guinea pigs by
Haterius and his colleagues.[19] Such grafts become attached to
the iris and, like similar homoplastic grafts attached to the
subconjunctival tissue, are composed mainly of basophils
about two months after transplantation. The ocular grafts in
hypophysectomized guinea pigs caused an increase in the
number of ovarian follicles with uterine hypertrophy and
persistent oestrus. No atrophy of the thyroid or adrenals oc-
curred. The authors point out that inadequate vasculariza-
tion and the absence of a nerve supply may account for the
lack of a secretion of luteinizing hormone (no complete fol-
licular maturation or ovulation or corpus luteum formation).
Martins (1936) found that pituitary transplants (in kidney
or in anterior chamber of eye) had little effect on the symp-
toms of hypophysial deficiency in five rats receiving the
transplants 16–100 days after hypophysectomy. Also he
transplanted the pituitary into gonadectomized nonhypo-
physectomized rats. Castration-cells could be found in the
pituitary *in situ* but not in the grafts 1–3 months later. The

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[19] Haterius, Schweizer, and Charipper (1935) and Schweizer, Charipper, and
Haterius (1937).

[27]

pars intermedia, which is the least vascular part of the pituitary, survived transplantation best.

Kasahara (1935) has studied the changes in the cells of the rabbit's pars glandularis when cultures are made of the latter. He found that the proliferating cells were neither chromophilic nor chromophobic. He described the cultured cells as "deflected epithelium" in distinction from Champy's term "dedifferentiated epithelium." Gaillard (1937) cultured juxtaposed slices of the pars glandularis and the pars neuralis of rats. He observed at the line of contact structural alterations including cysts, which led him to suggest that a similar relationship *in vivo* accounts for the morphological peculiarities of the pars intermedia. The same author described in another report (1937) cultures of the pars glandularis and other tissues removed from rabbits. Under proper conditions he could recognize oxyphils. He believed that suitably cultured anterior pituitary increases the rate of growth of osteoblasts. Anderson and Haymaker (1935) found that only the chromatosome-dispersing hormone from the pars intermedia is formed in cultures of the pituitary of rats eight days old. There was no evidence of new secretion of the diuresis-inhibiting hormone (pars neuralis) or of gonadotropic, thyrotropic, or adrenal cortical stimulating hormones (pars glandularis). Their results agree with those of Engel and Werber (1937) but not with those of Nagayama (1937), who was interested only in the formation of gonadotropic hormones. The observations of Geiling and Lewis (1935) are discussed in chapter viii.

SUMMARY

The blood supply of the pituitary body is complex. The hypophysio-portal veins, concerning which so much has been written, now appear to be afferent rather than efferent as thought formerly. They correspond, as far as the pars glandularis is concerned, to the hepatic portal veins. Also, like the liver, the anterior lobe is furnished with arterial vessels. The blood supply of the pars glandularis is quite independent

of that caring for the pars neuralis. At least in mammals like the monkey and man, it is now believed that there is no close vascular connection between the pituitary body and the hypothalamus. There is, therefore, little basis for postulating important effects of pituitary hormones on diencephalic centers.

However, certain hypothalamic centers, particularly the supraoptic nuclei, supply efferent fibers to the pars neuralis. If this innervation is completely severed, the pars neuralis atrophies and ceases to secrete its hormone in some if not all mammals. The cells of nuclei like the supraoptic nuclei morphologically are very different from most neurones but cannot yet be described as glandular cells of the diencephalon. The innervation and especially the central connections of the pars glandularis and pars intermedia are matters requiring intensive investigation.

The function and therefore the morphological significance of the pars tuberalis are unknown.

The pars intermedia, the source of the chromatosome-dispersing hormone in many animals, is, of course, a part of the pars buccalis. In certain animals lacking a pars intermedia, either because of its failure to differentiate or because of its regression in later life, the lobe's characteristic hormone is secreted by the pars glandularis.

The oxytocic and vasopressor hormones of the pars neuralis probably are not secreted or derived from cells of the pars buccalis such as invading basophils. Such invasion of the pars neuralis is not etiologically related to diseases like essential hypertension or eclampsia. Certainly, the hyaline bodies of Herring do not represent the hormones either actually or in a preformed state. A newly described glandular cell in the pars neuralis appears to be the source of the diuresis-inhibiting (vasopressor) hormone.

A great variety of changes in the pars glandularis has been related to the endocrine equilibrium of the animal, whether occurring normally or owing to a deficiency or to the injec-

tion of hormones. Generally accepted changes in the pituitary due to a hormone-deficiency are the appearance of thyroidectomy-cells following thyroid extirpation and the appearance of castration-cells following gonadectomy. In addition, there is good evidence that a deficiency of adrenal cortical hormone is accompanied by a marked reduction in the percentage of basophils. The morphological changes in the pituitary caused by gonadectomy can be corrected by oestrogenic and androgenic substances, but not by progesterone. Injected into normal animals, large doses of male or female hormone cause a depletion of the granules of the basophils. Very large doses of an oestrogen like oestrone bring about hypertrophy of the pars glandularis because of a hyperplasia of the reserve cells. This change may culminate in the formation of a reserve-cell adenoma.

Considerable progress has been made in relating the morphology of the pituitary to disease in man. Adrenal insufficiency is clearly accompanied by a marked reduction of the percentage of basophils. The syndrome of Cushing (pituitary basophilism) is invariably associated with hyaline changes in the basophils. A basophil adenoma is not necessarily present. The best-known syndrome etiologically related to the pituitary is acromegaly (and giantism); the change here observed is the development of an adenoma composed of oxyphilic cells. Hence oxyphils are thought to secrete growth-promoting hormone. The opinion of the most careful investigators is against the view that pituitary changes (especially in the basophils sometimes in relation to their growth into the pars neuralis) are characteristic of essential hypertension, eclampsia, Graves's disease, or diabetes mellitus.

<div align="center">ADDENDUM</div>

There appeared to be no great need in this volume for a chapter dealing only with the effects of hypophysectomy, inasmuch as almost all the topics would require reconsideration in the succeeding chapters. All the various effects of hy-

pophysectomy are referred to in the Index. However, there are a few reports which should be mentioned here. Abramovitz (1937), Thomas (1937), Miyagawa (1936), and Harris and Popa (1938) have discussed the technic of hypophysectomy in teleost fishes, in the mouse, and in the rabbit. A brief description of the effects of hypophysectomy in the mouse (in male and in normal, pregnant, and lactating female) will be found in the report of Leblond and Nelson (1937). Observations on the effects of radon or X-rays on the pituitary of various animals have been published by Bertolotto (1935), Cucchini (1934), Fehr (1936), Lacassagne and Nyka (1934-35), and Franck (1937). Karlik and Robinson (1935) gave a detailed description of the changes in the central nervous system as well as the other better-known alterations in the organs and their functions appearing in a dog during and after a five-year period following hypophysectomy. According to Robinson (1937), hypophysectomy in the pig is followed by characteristic atrophic changes in all the glands of internal secretion except the adrenal cortex. Certainly this observation requires confirmation.

The relationship of the hypothalamus to the pituitary body likewise is discussed in the appropriate chapters, especially in chapter x. Readers who are particularly interested in this relationship are referred to the review of Raab (1936). Raab's enthusiasm, however, has led him to many conclusions lacking a sound foundation.

CHAPTER II

THE REGULATION OF GROWTH BY THE PITUITARY BODY

NO INVESTIGATOR has succeeded in preparing a satisfactorily "pure" growth-promoting extract of the pituitary body. There is general agreement that the pituitary, among endocrine glands, is the most important regulator of growth; but whether this regulation is effected by a specific "growth-promoting hormone" or by direct or indirect combined effects of other pituitary hormones, such as the lactogenic and the thyrotropic hormones, remains an undecided issue.

Particularly Riddle and his colleagues oppose the view that a specific growth-promoting hormone is secreted by the anterior pituitary. They suggest that the combined action probably of the thyrotropic and lactogenic hormones accounts for the principal somatic effects of growth-promoting extracts and have put forward suggestive but not conclusive evidence in favor of this view. All the potent extracts which they have examined contained both of these hormones to which they attribute any calorigenic effects such extracts may have (Riddle and others, 1936). Bates and his co-workers (1937) found that the injection of "relatively highly purified preparations" of the lactogenic hormone into hypophysectomized pigeons caused body-growth as well as a marked increase in the weight of the liver.[1] Similar effects together with a growth of the intestine were observed in normal pigeons. The only studies which have been consid-

[1] Effkemann and Herold (1935) concluded that extracts of organs other than the pituitary may cause moderate or marked hypertrophy of the liver in the pigeon and rat without striking associated changes in body-weight. However, they believed that pituitary extract brought about specific morphological changes.

ered successful in mammals were made in mice with heredi-
tary dwarfism. According to Riddle (1935), and Bates,
Laanes, and Riddle (1935), growth in such mice can be pro-
duced by thyrotropic extracts or, much less effectively, by
lactogenic extracts. They observed a marked synergism of
the effect if both extracts were administered. "Follicle-stimu-
lating hormone," from the blood of the pregnant mare, was
without action. Kemp and Marx (1936) agreed that lacto-
genic extracts produce a definite growth of mice with heredi-
tary dwarfism. They found thyroxine more effective than
thyrotropic hormone, especially in combination with a pitui-
tary growth-promoting extract. It is of interest that the
degenerative changes in the gonads of such mice were cor-
rected and that normal gonads were maintained by a variety
of treatments—growth-promoting extract or lactogenic ex-
tract or thyrotropic extract or thyroxine.

However, there are numerous objections to the view that
the thyrotropic hormone or the lactogenic hormone or both
account for the principal effects of growth-promoting ex-
tracts. Conclusions drawn from experiments in pigeons prob-
ably have only a limited significance in mammals. Thyro-
tropic hormone antagonizes the growth-promoting effect of
the lactogenic hormone in pigeons (Bates, Riddle, and Lahr,
1937), whereas the two hormones were found to have a syner-
gistic effect on growth in the dwarfed mouse. Hypophysec-
tomized rats are very sensitive toward pituitary growth-
promoting extracts; yet no investigator has succeeded in
causing such animals to grow by administering either lacto-
genic hormone or thyrotropic hormone or a combination of
the two. Although it must be admitted that partially refined
growth-promoting extracts are usually more certain and more
persistent in their action than highly purified preparations,
the same remark applies to comparisons of the action of such
partially refined extracts with that of the combined adminis-
tration of lactogenic and thyrotropic hormone to mice with
hereditary dwarfism. Bates, Laanes, and Riddle (1935) ob-

served that the maximum effect on the growth of dwarfed mice was obtained by administering a growth-promoting extract ("Phyone") which had been only partially purified and contained lactogenic, thyrotropic, and gonadotropic hormones. Moreover, some authors have reported success in extracting from the anterior pituitary a growth-promoting principle free from gonadotropic hormone (Evans and others) or gonadotropic and thyrotropic hormones (Collip, Selye, and Thomson) or lactogenic and thyrotropic hormones (Dingemanse and Freud, 1935).

Some years ago Smith pointed out that the growth which occurred in hypophysectomized rats following the administration of a crude anterior pituitary extract was accompanied by no betterment of the atrophic changes in the thyroid, adrenal glands, and gonads. Also, it is agreed that the growth response to pituitary extract is not reduced as a result of thyroidectomy; in fact, acromegalic-like changes in the bones and joints of guinea pigs receiving anterior pituitary extract may be more pronounced in thyroidectomized than in normal animals (Silberberg, 1936; Silberberg and Silberberg, 1937). Mortimer's observations (1937) suggested that thyroid extract or thyrotropic hormone tends to cause a loss of minerals from certain bones, whereas growth-promoting extract may bring about a sclerosis. According to Moon (1937), suitably large doses of adrenotropic extract inhibit the somatic growth of gonadectomized animals without clearly affecting the growth of the spleen, kidneys, liver, and gastrointestinal tract; therefore, his results are in agreement with the view that effects on the adrenal cortex play no positive role in the general growth-promoting effect of a pituitary extract.

The only sensible verdict to render in answer to the plea that the anterior pituitary elaborates (or does not elaborate) a specific growth-promoting hormone is the Scotch verdict of "not proved." Although the thyroid, gonads, and adrenals undoubtedly are important in the regulation of growth, it appears unlikely that changes in the secretory performance of

these glands account for the growth-promoting effects of anterior pituitary extract. Future work must decide the significance of the lactogenic hormone in growth, as far as growth is affected by the pituitary body. Also, without confirmation, it is hazardous to affirm or deny either that "growth-hormone" free from lactogenic (and other) hormone can be prepared or that a suitable combination of anterior pituitary "hormones," with little effect separately, can imitate all the growth-promoting effects of a suitable anterior pituitary extract. Therefore, the reader should recognize that the use of the term "growth-promoting hormone" in other parts of this chapter and book is dictated by convenience rather than by a belief that it deserves more than a qualified acceptance.

Recent reports on visceral or somatic abnormalities caused by hypophysial deficiency.—Schofield and Blount (1937) observed that the removal of the anterior pituitary from larvae of *Amblystoma punctatum* is followed by a general reduction in growth, including the growth in length of the digestive tract. They believed that the latter change is causally related to the former. The reports of other investigators, previously reviewed, indicated that hypophysectomy in larval or immature salamanders of a closely related species (*A. tigrinum*) does not significantly affect growth. Aubrun (1935) removed the pars glandularis or the neurointermediate lobe from *Bufo arenarum* and observed cutaneous changes—hyperkeratosis and lessened secretion, or paling and capillary dilatation—resembling those previously described by Giusti and Houssay.

Only a few reports dealing with mammals need be considered here. Houssay and Lascano Gonzales (1935) studied the effects of hypophysectomy on the dog's spleen. In the young dog, splenic growth was reduced; in the adult dog, splenic atrophy appeared to be associated with an increase in the size of the splenic follicle and an increase in the number of malpighian corpuscles. The authors considered that the changes resembled those characteristic of senility. The re-

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port of Freud (1935) on the rapidity of atrophy of certain endocrine organs after hypophysectomy is of interest to investigators. According to this author, complete hypophysectomy in the rat is followed by a maximum atrophy of the gonads in 8–10 days, of the secondary sexual organs in 8–25 days, of the thyroid in 10 days, and of the adrenals in 14–18 days. Lüth's report (1937) indicated that spontaneous hypophysial deficiency in man (Simmonds' disease) may occur independently of genetic constitution. He discovered cases of apparent hypophysial deficiency in individuals with normal identical twins.

The effects of growth-promoting hormone (anterior pituitary extract or tissue).—There is a number of recent observations, some clear cut, some difficult to classify otherwise, which bear on the physiology and pharmacology of the growth-promoting hormone. Murayama, Gurchot, and Guttentag (1937) concluded that a high concentration (2–4 per cent) of a commercial growth-promoting extract inhibits the root-growth of seedlings of *Lupinus albus;* nothing in the report indicates that this is a specific effect either of growth-promoting or, indeed, of anterior pituitary extracts. Fresh fowl pituitary was inserted into incubating hen's eggs by Pighini (1937) on the third to the fifth day of incubation. The tissue was absorbed and appeared to favor embryonic growth (seventeenth day of incubation). However, Wolff and Stoll (1937) believe that embryonic growth and differentiation, including the endocrine organs, takes place in the fowl in the absence of a functional pituitary body. All the other experiments were performed in mammals. Several investigators have found that the administration of anterior pituitary extract to pregnant animals, such as the rat, may prolong gestation and promote fetal growth; however, it usually appeared that such changes should be attributed to gonadotropic—abnormally prolonged secretion by corpora lutea—rather than to growth-promoting hormone. Recently, Watts (1935) reported that she was able to cause a significant increase in the

weight of both fetuses and mother by administering certain growth-promoting extracts to pregnant rats. Greep (1936) studied the replacement value of pituitary grafts inserted into the sella of rats of both sexes immediately after hypophysectomy, which was performed when the animals were four weeks old. He obtained partial replacement in about three-fourths of the animals (5 males and 32 females), in that growth occurred but did not proceed beyond one-half to two-thirds the normal adult level. The performance of the sexual glands was often essentially normal and will be discussed in chapter iii.

Especially among clinicians there has always been considerable interest in the changes in bones and joints attributed to alterations in the secretory activity of the anterior pituitary. Recently Coryn (1936) has reviewed from a clinician's viewpoint the etiological relationship between diseases of bones and joints and changes in the endocrine glands. He concluded that pituitary hyperfunction—e.g., oxyphil adenoma of acromegaly—accelerates cellular proliferation and only in this way affects endochondral osteogenesis. He denied that any secretion of the normal or abnormal anterior pituitary alters hyaline cartilage or causes hypertrophy of cartilage cells or calcification of osseous tissue. Also, he believed that ankylosing or deforming arthritides do not result from a disturbance of pituitary function, contrary to experimental and clinical observations of others. Silberberg (1936), as well as Silberberg and Silberberg (1936–37), recently have studied the changes in the bones and joints of guinea pigs receiving daily injections of an acid extract of the anterior pituitary of the ox for 1–20 weeks. The authors concluded that it is thus possible to produce changes in the joints and in the chondro-osseous junctions of the ribs resembling acromegalic arthropathia and acromegalic rosary. Also, they found that callus-formation was delayed by the administration of the extract. All these changes were equally or more pronounced in thyroidectomized guinea pigs. The reader is

referred to the authors' publications for a detailed account of their findings, which include observations of the effects of such an extract on other phases of bone-growth in normal and ovariectomized animals. Mortimer (1937) carefully studied the changes in bones, especially those of the cranium of the albino rat, resulting from hypophysectomy or from the administration of growth-promoting extract. His observations cannot be adequately summarized in a few words, but should be read in the original communication by those who are interested in the endocrine phase of bone-growth and maintenance.

It will be recalled that the principal gross biochemical changes in the bodies of normal rats, receiving growth-promoting hormone compared with littermates not so treated, consist of a diminution in the percentage of "fat" and an increase in the percentage of water, protein, fat-free dry tissue, and ash. Lee and Ayres (1936) have recently studied some of the similar biochemical aspects of hypophysectomy in sixteen pairs of littermate rats, one of each pair being hypophysectomized at a weight of about 210 gm. All the animals received the same food in the same quantity. The weight loss of the hypophysectomized rats was about 20 per cent greater than that of the normal rats; however, the normal animals lost more fat (60 per cent loss compared with 28 per cent loss in operated rats).[2] There was a 20 per cent loss of body nitrogen in the hypophysectomized rats, whereas there was no loss in the normal group. The percentage of creatine and creatinine in the carcass was the same in both groups. In general, the changes observed in hypophysectomized rats were the reverse of those following injections of growth-promoting extract. Lee and Ayres also studied a number of nitrogenous constituents, both protein and non-protein, of the liver. The only conspicuous changes were in the total non-protein nitrogen, amino acids, and urea, all of which were present in higher concentration in the liver of the hypophy-

[2] Substances extracted by ether.

sectomized animal. According to Reiss, Schwarz, and Fleisch-mann (1936), the administration of growth-promoting ex-tract (containing some adrenotropic but no thyrotropic or gonadotropic hormone) to the starved dog or rabbit causes, even after a few hours, a considerable fall in the "rest" N (10–49 per cent) and free arginine (19–43 per cent) associated with a rise of 21–66 per cent in the urea N of the blood. Their results are not fully in accord with those previously reported by others. In a study of the phosphatase activity of bone and kidney, Wilkins and others (1935) were unable to detect any significant difference in adult female rats, some of which re-ceived injections of a potent growth-promoting extract. Body, bone, and kidney weights were all increased as a result of the treatment.

The relationship between the growth-promoting hormone and other glands of internal secretion. 1. *The gonads.*[3]—Perhaps the simplest interpretation of the effect of gonadectomy on growth in certain animals is that the effect is principally due to a change in the secretory activity of the anterior pitui-tary. Recently, studies of growth-alterations following gonad-ectomy in the rat have been reported by Holt, Keeton, and Vennesland (1936), Billeter (1937), Freudenberger and Hashimoto (1937), and Freudenberger and Howard (1937). Castrated and normal male rats gow at about the same rate; however, the normal male tends to grow larger. The spayed female rat clearly grows more rapidly and maintains its weight better than the normal female. The difference is not due to the deposition of fat and may amount to 20 per cent at an age of 13 weeks (9 weeks after spaying). The glands of internal secretion as well as other viscera are heavier; the most striking change is in the thymus which may be 75 per cent heavier than that of the normal female.

At least in the case of the female rat, the internal secre-

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[3] Growth-promoting extract, like others derived from the anterior pituitary, may contain a substance inhibiting certain gonadotropic effects. This substance has been named "pituitary antagonist" by Evans and is discussed in chap. iii.

tions of the ovary appear to inhibit the secretion of growth-promoting hormone by the pituitary. This belief is further strengthened by the observation of Spencer, D'Amour, and Gustavson that the repeated injection of oestrone into growing rats significantly inhibits growth. Their experiments have been extended by Zondek (1936–37), Billeter (1937), and Freudenberger and Clausen (1937).[4] Small doses of oestrone, such as 3 rat-units daily, inhibit the growth of spayed rats so that they may weigh less than non-injected spayed rats and, often, less even than normal non-injected rats. However, such small doses must be given from an early age and have little effect if first injected when growth is nearing completion. The inhibition of growth due to larger doses of oestrone (e.g., 0.02 mg. on alternate days) affects the glands of internal secretion and, with the exception of the liver, almost all the other viscera including the central nervous system. Zondek used large doses of oestradiol benzoate in his experiments (e.g., 180,000 mouse-units of "Dimenformon" in 18 weeks). He concluded that the dwarfing of rats by this treatment was caused by a marked hypophysial deficiency, which in some cases was complete, inasmuch as no further growth occurred after treatment was stopped, unless anterior pituitary growth-promoting extract was injected. Zondek, also, performed experiments with fowls in which he observed osteosclerosis (femur, tibia, and fibula).[5]

2. *The thyroid.*—The possible importance of the thyrotropic hormone as a participant in the growth effects of anterior pituitary extract has already been discussed. There can be no question concerning the inhibition of growth which may appear if complete thyroid deficiency is produced early in life—a statement again emphasized by the recent study of

[4] Shumacker and Lamont (1935) were unable to detect any change in the growth of 6 rats receiving 9 rat-units of oestrone daily between the ages of 23 and 90 days.

[5] Numerous other observations on the effects of oestrogens on the pituitary and its secretions are discussed elsewhere (particularly chaps. i and iii). Lauson, Heller, and Sevringhaus (1937) studied the effects of an oestrogen in the mature spayed rat. They particularly investigated the pituitary, adrenals, and thymus.

Binswanger (1936), who performed his experiments in dogs. There is real doubt, however, that the thyrotropic hormone which may be found in growth-promoting extracts is of great importance so far as growth effects are concerned.[6]

3. *The adrenals.*—Moon (1937) found that the injection of the anterior pituitary hormone stimulating the adrenal cortex inhibits somatic growth in young rats of both sexes (the author administered 13–42 "units" over a period of 2–4 weeks). There was little or no effect on the growth of the spleen, liver, kidneys, and alimentary canal. Swingle and others (1936) increased the period of survival of adrenalectomized cats by administering a growth-promoting pituitary extract; however, they attributed the beneficial effect of the extract to gonadotropic hormone rather than to a growth-promoting hormone.

4. *The thymus.*—The more recent observations suggest that an internal secretion of the thymus promotes growth and development. However, there are no observations indicating to what extent such an action may be related to the secretion of a growth-promoting hormone by the pituitary. Rowntree, Clark, and Hanson (1935) reported that the administration of an extract of the thymus to rats through several generations finally led to precocious growth and development which might be very marked early in life. The reverse experiment, thymic deficiency by thymectomy, produced after 2–3 generations a retardation of early growth, especially marked at an age of about 1 month (Einhorn and Rowntree, 1936). The rate of development appeared not to be affected. Parhon and Coban (1936) also found that thymectomy retards the growth of fowls (Leghorn and Rhode Island varieties). They removed both lobes of the thymus when the birds were about 3 weeks old; at an age of 6 months the thymectomized fowls weighed about 30 per cent less than the nonoperated controls.

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[6] The growth of the liver in the duck in relation to the thyroid, gonads, and hypophysis is discussed by Benoit (1937).

5. *The epiphysis.*—Engel (1936), as well as Kup (1936), continues to champion the view that a pineal secretion inhibits the growth-promoting effects of anterior pituitary secretion. However, the evidence which they are able to assemble does not enable one to attach even hypothetical value to this belief. Some observations suggest the opposite effect. For example, Takács (1935) fed dried calf epiphysis to young fowls (10–35 mg. per day). The birds receiving epiphysis for 4 months weighed more than 200 per cent more than the controls. The excess weight was striking (102 per cent) but less pronounced after 5 months' feeding, when the experiment was terminated.

Deficiency of vitamins or minerals and the growth-promoting hormone.—It appears that failure of growth due to a deficiency of vitamin A or of the "growth factor" of casein cannot be attributed to a failure in secretion of growth-promoting hormone. This is indicated by the experiments of Margitay-Becht and Wallner (1937). The authors produced growth stasis in young rats by diets deficient either in vitamin A or in the alcohol-ether extract of casein. In neither case did the administration of anterior pituitary growth-promoting extract cause a resumption of growth. There remains, of course, the possibility that the dietary deficiency had rendered the tissues refractory toward the hormone.

Orent-Keiles, Robinson, and McCollum (1937) concluded that a sodium-deficient diet, more than diets deficient in Cl or NaCl, interferes with growth in the rat. Whether or not this change as well as others, particularly in the female organs of reproduction, depends to an important extent on changes in the anterior pituitary is not known. According to Hove, Elvehjem, and Hart (1937), zinc appears to be an important factor in the secretion or peripheral action of a pituitary hormone controlling (favoring) the movement and tone of the digestive tract of the rat. With a deficiency of zinc in the diet and therefore with a deficiency of this hypothetical hormone, intestinal absorption is delayed and reduced so

that growth is retarded. The protein phase of metabolism appeared particularly to be reduced. The authors' dismissal of the growth-promoting hormone as the important factor is largely based on the greater effect of whole pituitary implants in comparison with that of a growth-promoting extract ("Antuitrin G"). However, the comparison was made under different conditions as to the age of the rats and the duration of zinc-deficiency. Therefore, until growth-promoting hormone or other better-defined anterior pituitary hormones have been clearly excluded, it is undesirable to identify a new pituitary hormone on so slender a basis.

The effect of growth-promoting hormone on the growth of neoplasms.—Engel (1935) has made further observations on the relationship of the pituitary and of gonadotropic hormones (prolan, gonadotropic hormone of pregnant-mare serum) to the growth of transplants of Ehrlich's adenocarcinoma in mice. He concluded that gonadotropic hormones may have some inhibiting effect on the growth of the tumor and that pineal extract may have a marked inhibitory effect. He believed that the depressing effect of pineal extract is indirect and due to a secretory inhibition of, or antagonism toward, the growth-promoting hormone. Several recent authors agree that hypophysectomy retards the growth of malignant neoplasms, especially if transplantation is delayed several weeks after operation (Walker mammary carcinoma: Samuels and Ball, 1935; neoplasm due to 1:2:5:6 dibenzanthracene: Ball and Samuels, 1936; transplanted neoplasm: Reiss, 1936). Reiss found that the oxygen-consumption of such tumors is low, but that aerobic glycolysis remains unchanged or increases. Emge and Murphy (1936), investigating the growth of autogenous sarcoma in the rat, observed no striking effect of hypophysectomy on tumor-growth except when transplantation was undertaken some time after operation. They could detect no increased rate of tumor-growth as a result of the administration of growth-promoting extract to tumor-bearing normal or hypophysectomized rats. Likewise

Zondek (1937) concluded that the secretion of growth-promoting hormone does not influence the growth of a sarcoma due to benzpyrene; for the tumor grew no better in normal rats than in rats dwarfed because of the injection of large doses of oestradiol benzoate.

Druckrey (1936) believed that pituitary gonadotropic hormone inhibits tumor-growth in the rat. As malignant neoplasms he used the Flexner-Jobling carcinoma and the Jensen sarcoma. Shortly after castration, tumor-growth appeared to be unusually rapid. Later, however (4–6 months after castration), when the gonadectomized animal's pituitary contains and secretes the maximum amount of gonadotropic hormone, inhibition and even failure of tumor-growth appeared. Largely from this finding Druckrey reached the conclusion stated above.

Both recent and older observations permit the drawing of only limited conclusions as to the control of the growth of neoplasms by the anterior pituitary. If there is a complete pituitary deficiency, the initiation of neoplastic growth is more difficult; if the deficiency is produced after neoplastic growth is under way, further growth may take place at a slower rate. Certainly the pituitary appears not to be an important regulator of cellular proliferation in tumors. The conclusion of Engel—that pineal extract inhibits the growth of a carcinoma by acting on the pituitary—as well as the inference of Druckrey—that the growth of a sarcoma or carcinoma is inhibited by the secretion of gonadotropic hormone—hardly deserve acceptance without data from more complete experiments.

The assay of growth-promoting extracts.—Several matters of technic must be mentioned in connection with the assay of growth-promoting extract. Evans, Pencharz, and Simpson (1935) pointed out that crude rather than purified extracts seem to have more certain effects and may be active if given to animals no longer responding to a purified extract. Also, Mortimer (1937) found "resistance" appeared later toward

crude extracts than toward more purified extracts. It is difficult to correlate these observations with the conception of "antihormones."

Evans and his colleagues found that if hypophysectomized rats failed to respond to an extract, there might occur a striking response if glucose solution was also administered parenterally.[7]

Factors influencing the assay of growth-promoting hormone have been studied in normal and hypophysectomized rats by Chow, Chang, Chen, and van Dyke (1938). In normal rats, in confirmation of the work of others, they found the young adult female rat most suitable. Sex does not affect the response of hypophysectomized rats which, in terms of the percentage change in weight, is at least twice as great as that of normal rats. Rats with a hypophysial deficiency of 8–10 months are less sensitive than those hypophysectomized 1–6 months before assay. Differences in response in relation to dosage are more easily recognized in hypophysectomized rats, whereas in normal rats a doubling of the dose may not be followed by a change in response which is convincingly greater. In either normal or hypophysectomized rats the optimum period of injection probably is not longer than 10 days. Even 6 weeks after the use of rats for assay, their response to a second course of injections is reduced.

The preparation and purity of growth-promoting extracts of the anterior pituitary.—The only recent attempts to purify growth-promoting extracts are those of Dingemanse and Freud (1935). They stated that their preparation contained neither lactogenic nor thyrotropic hormone and that 0.025 mg. administered intraperitoneally once daily to hypophysectomized rats (120–80 gm.) caused an average gain of weight amounting to 7 gm. following administration for one week. The method they described required the following

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[7] According to Shelton, Cavanaugh, and Long (1935), the effect of growth-promoting extract in adult female rats is potentiated by the injection of 0.5 cc. of human serum 3–6 weeks previously.

steps: adsorption on norit from a weakly alkaline solution, elution of the hormone by phenol, and subsequent precipitation by a solution of one part of alcohol in two parts of ether. The authors also concluded that the hormone could dialyze through collodion membranes and that the nitrogen content of the material in the sac was higher than that of the dialyzed material. The dialysis was performed at a very high pH (0.01 N NaOH).

Summary.—The clear-cut identification of a growth-promoting hormone in the anterior pituitary is perhaps the problem of greatest immediate importance to those interested in this aspect of the physiology of the pituitary body. On the other hand, if such a hormone is not secreted by the gland, new interpretations of much satisfactory data will have to be made. It is still possible, however, provisionally to use the term "growth-promoting hormone."

Few of the recent observations require reference in this summary. Experimentally, changes in bones and joints, some resembling those of acromegaly, have been more extensively studied. Additional data on general biochemical changes due to hypophysectomy have been secured. As far as other glands of internal secretion are concerned, there is additional evidence, at least in the rat, that the oestrogenic secretion of the ovary may act as a brake on general growth. Endocrine glands such as the thyroid, adrenals, thymus, and epiphysis may affect growth—sometimes positively, sometimes negatively. How such effects are related to excessive or reduced secretion of the growth-promoting hormone in no case has been convincingly demonstrated. The growth of malignant neoplasms may be slightly favored by anterior pituitary secretion; this effect, however, appears not to be important. Recently little attention has been paid to the purification of the growth-promoting hormone. This may prove to be an impossible task made even less attractive by the difficulties of accurate assay.

THE GONADOTROPIC HORMONES OF THE
PITUITARY BODY

I F THE number of articles published were acceptable as
a safe basis of judgment, it could easily be concluded
that the gonadotropic hormones are the most important
secreted by the anterior pituitary. This field of inquiry is
attractive not only because of its inherent importance but
also because the probability of securing fruitful results is
great. There can be no doubt that the anterior pituitary
secretes gonadotropic hormone(s) essential for the normal
functioning of the gonads of mammals and other vertebrates.
As a result, nearly every investigator interested in the physi-
ology of the gonads has quickly entered or wandered into
the rich and diversified field of pituitary-gonad interrelation-
ships—sometimes without realizing he is there. Furthermore,
work may be greatly facilitated by the fact that the assay
of the hormones with a fair degree of accuracy is often, but
not always, easily accomplished.

Despite all the labor represented by a vast number of re-
ports during the past few years, it is not yet possible to
enumerate satisfactorily the gonadotropic hormones of the
pituitary. Separate follicle-stimulating and luteinizing hor-
mones are generally believed to exist; it is by no means cer-
tain that the former specifically maintains the mammalian
seminiferous tubules, whereas the latter insures the normal
secretion of testicular hormone by the interstitial cells. It
has been reported that principles synergizing with or an-
tagonizing gonadotropic hormone have been extracted from
the pituitary; however, their physiological importance is
largely postulated from deduction. Several authors have rec-
ognized the great importance of excluding the animal's own

pituitary in determining accurately qualitative and quantitative effects of extracts. The increased accuracy of interpretation more than justifies the great increase of labor required. Final judgment on the effect(s) of an extract should be based upon experiments with hypophysectomized animals.

The follicle-stimulating hormone often excreted in human urine in considerable amounts after spaying or castration or after the menopause probably originates in the anterior pituitary. On the other hand, the gonadotropic substances discussed in chapter iv appear not to be secreted by the hypophysis. These substances are prolan (from the chorionic cells of the human pregnant uterus), the gonadotropic hormone characteristic of pregnant-mare serum (likewise probably secreted by chorionic or endometrial cells), and the gonadotropic hormones of neoplasms such as hydatidiform mole, chorionepithelioma, and testicular tumor (from the cells of the neoplasms).

In this chapter a systematic account of pituitary-gonad interrelationships, especially as these are understood from later work, will be attempted. It is hoped that the reader will recognize the diversity of the literature both in subject matter and in quality. Diversity in the former often makes arrangement difficult. Diversity in the latter may lead to definite conclusions, either sound or wrong. Sometimes, however, the only reasonable position to take is one of suspended judgment, unwelcome as this may be to many readers.

THE BIOLOGY OF THE GONADOTROPIC HORMONES IN VERTEBRATES

Fishes.—Using an extract of ox pituitary, Young and Bellerby (1935) were unable to produce either significant changes in the gonads or metamorphosis in the lamprey (*Lampetra planeri*). However, changes in body-shape and marked cloacal swelling, both secondary sexual characteristics of the period preceding spawning, appeared. In earlier reports several authors had succeeded in producing spawning

or hypertrophy of the gonads in other fishes. Usually changes in the gonads or secondary sexual organs of fishes, including spawning, can be produced by fish pituitary but not by mammalian pituitary or by extract of the mammalian pituitary. However, dosage may not have been adequate. Descriptions of experiments and references to other work can be found in the reports of Gerbilsky and Kashchenko (1937) and of von Ihering and de Azevedo (1937). Artemoff (1936) successfully used the pituitary of the frog.

Amphibia.—The majority of the reports previously reviewed indicated that the amphibian pituitary has an importance in the maintenance of the gonads corresponding to that in mammals. The most that will be attempted here is to bring the references up to date by citing the work of recent authors.

1. *Anuran amphibia.*—Several aspects of the biology of gonadotropic hormones have been studied in six species of frogs (*Bombinator igneus*,[1] *Hyla arborea*,[1] *Pelobates fuscus*,[1] *Rana esculenta*,[1] *R. pipiens*,[2] and *R. temporaria*[3,4]). Several authors have studied ovulation or oviposition or both. Rostand administered the extract of 6–20 pituitary glands of the same species to *R. esculenta*, *R. temporaria*, or *Bufo vulgaris*. He found that ovulation could be produced 5 months before the normal time. It was more difficult to induce ovulation earlier; moreover, the ova then were often not mature and could not be fertilized. Similar results were reported by Gallien who used *R. temporaria*. The number of eggs extruded appeared to be proportional to the dose of frog pituitary (6–9 glands as a saline extract) or beef anterior lobe (1.6–3 gm. as an alkaline extract). The very low potency of the pituitary of the ox was previously reported by others (e.g., Rostand using *H. arborea*). Gallien observed no effect from the injection of urine of spayed women (3–8 cc.) or urine of pregnancy (7–9 cc.). According to Rostand, extract of the pituitary of *R. esculenta* or *Bufo vulgaris* can readily induce

[1] Rostand (1934–35).   [2] Rugh (1937).   [3] Gallien (1937).   [4] Shapiro (1937).

ovulation in *H. arborea* but not in *Bombinator igneus*, unless the ovary contains ripe ova. He found *P. fuscus*, even when the ovaries contained ripe ova, very insensitive toward either type of pituitary extract.[5]

Rugh concluded that the anterior pituitary of the male frog (*R. pipiens*), although somewhat heavier than that of the female, contains little more than half the amount of ovulation-inducing hormone. He stated that usually within 24 hours oviposition in mature frogs followed the intraperitoneal administration of the pars glandularis of two adult females or four adult males. In the hibernating male frog of the same species, Rugh found that about 16 hours after the administration of anterior pituitary gonadotropic hormone, amplexus (with an ovulating female of the same species only) and the release of all mature spermatozoa could take place. Spermatozoa were found in the lumen of seminiferous tubules, in Bowman's capsule, the renal tubules, and the ureter. In another article, Rugh reported on seasonal changes in ovarian and pituitary weight and the relationship of such changes to alterations in pituitary gonadotropic effects. Shapiro (1936–37) has particularly studied the clasping reflex in *R. temporaria* and *Xenopus laevis* (a toad). He decided that secretions of both the pars glandularis and the testis or ovary are necessary for the initiation of the reflex. The reflex, followed by ovulation, oviposition, and fertilization, could be produced in *Xenopus* by the injection of pregnancy-urine extract or an acid extract of the pars glandularis of the sheep or goat. In *B. arenarum* the removal of the pars glandularis a few days after subtotal extirpation of testis tissue prevents the marked compensatory growth of the latter (Houssay and Lascano-Gonzalez, 1935).

The implantation of pituitary tissue of the frog or toad can cause ovarian stimulation in the immature mouse (Benazzi, 1937; and Zwarenstein, 1937). However, the potency of amphibian pituitary is much less than that of mouse pituitary.

[5] See also Osima (1937).

Shapiro (1937) attributed the inhibiting or stimulating effects of an extract of sheep pituitary, used chiefly for its lactogenic effects, to contaminating gonadotropic hormone. The author studied the extract's effects on the amphibian testis.

2. *Urodele amphibia.*—Adams and Mayo (1936) investigated the effects of homo-implants on oviposition in a salamander, *Triturus viridescens.* They were able to produce oviposition in the nonbreeding months stretching from October to early March. The effect appeared earlier at 20° than at 14° C. (resembling the observation of Bellerby in *X. laevis;* Bellerby used beef anterior-lobe extract). The male pituitary was perhaps the more potent; the pituitaries of animals gonadectomized 4–98 days previously were possibly, but not definitely, more potent than normal glands. Kleinschmidt (1937) studied the changes in the male gonads of hypophysectomized larvae of *T. vulgaris* for many months postoperatively. Although regressive changes in the germinal cells of the testis were clearly marked, especially 3–10 months after hypophysectomy, yet 20 months postoperatively islands of healthy cells with spermatogonia, resembling normal testicular tissue of animals four months old, could be found. The Wolffian and Müllerian ducts were both well developed; however, the latter was not joined to the cloaca. Some degenerative changes in the follicle-cells of the testis were found. The fat body was not altered until an age of 14 months, after which it underwent hypertrophy because of hyperplasia.

Reptiles.—According to Evans (1935), the gonads of immature young lizards (*Anolis carolinensis*) of either sex could be stimulated by prolan or by extract of whole sheep pituitary. In the male the same effects were produced by either extract: testicular hypertrophy, hypertrophy of the hemipenis, epididymis, and vas deferens, spermatogenesis, elevation of the dorsal crest, frequent molting, behavior changes, etc. In female animals prolan brought about hypertrophy of the ovary and oviduct as well as more frequent molting and

behavior changes. Only sheep pituitary extract caused, in addition to these changes, maturation of ova or ovulation and oviposition. Mellish (1936) investigated pituitary-gonad interrelationships in the horned lizard, *Phrynosoma cornutum*. Prolonged illumination of animals furnished abundant food and kept at a high temperature (35° C.) for six weeks during winter had little effect on the gonads (control lizards hibernating at 5° C.). On the other hand, if the experimental animals were also given the equivalent of 3 gm. of whole pituitary of the pig, the gonads of both sexes were stimulated so as to resemble those of animals early in the breeding season. Other experiments in similar lizards have been reported by Mellish and Meyer (1937). An increased ovarian weight, largely due to an increased deposition of yolk, was produced by the administration of various anterior pituitary extracts or pregnant-mare serum. The animals were well fed and kept at 32° C. under continuous artificial illumination. None of the animals was hypophysectomized. An unfractionated anterior pituitary extract did not affect the ovaries of animals hibernating at 5° C. At that temperature there appeared to be only partial absorption of the extract.

Forbes (1937) investigated the action of an alkaline extract of whole pituitary of sheep in immature alligators (4–18 months after hatching). Some hypertophy of the ovaries together with marked growth of the oviducts occurred in female animals. There was no effect on the Wolffian ducts. In males a marked hypertrophy of the testes, without spermatogenesis, was produced. The size of the mesonephron in males receiving the extract was reduced.

Birds.—In the past few years there has been reported a considerable number of new or more detailed observations on the physiology of gonadotropic hormones in birds. Almost all deal with hormones of pituitary origin.[6] An interesting as-

[6] Later reports also support the conclusion that prolan has no significant effect on the gonads of birds (Hill and Parkes, 1935; Witschi and Keck, 1935; Uhl and others, 1937). Breneman's results (1936) apparently were inconclusive. Koch (1935) could not confirm his earlier report that prolan brings about an increase in the egg-laying performances of hens.

pect of work in this field is the manner in which the duration, intensity, and quality of light may affect the reproductive organs of both birds and other vertebrates. There is every likelihood that such effects of light are mediated through the pars glandularis; moreover, such effects are additional evidence in favor of the physiological importance of efferent secretory fibers, innervating the anterior pituitary. In the account which follows, recent general work in birds will be considered first. At the end of this section the effects of light on the sexual organs of other vertebrates, including mammals, will be discussed.

Domm and Dennis (1937) caused definite changes in the gonads of chick embryos by administering sheep pituitary extract (see Fig. 9). Five rat-units were administered daily during the 5–9 days of incubation, the embryos being removed later (e.g., the eighteenth day). In female embryos there occurred hypertrophy of the ovary (chiefly of the medulla) and rudimentary right gonad. (Injections during post-embryonic life did not produce the latter effect.) Testicular hypertrophy in male embryos was less frequent and less pronounced; when present it was due principally to a change in interstitial tissue. Alterations of the Müllerian or Wolffian ducts or of the head furnishings did not occur. Hybrid embryos responded better than pure-bred Leghorns. Breneman (1936) studied the effects of follicle-stimulating and luteinizing hormones on the gonads of chicks 5–15 days after hatching.[7] The author's experiments were often complex, and some of his conclusions appear not to be firmly established. Maximum gonad-stimulation was produced by pituitary follicle-stimulating hormone or pregnant-mare serum. He believed that, as in the mammal, the follicle-stimulating hormone affected the tubules of the testis, whereas the luteinizing hormone acted on the testicular interstitial cells. Also,

[7] The lactogenic hormone, which according to Riddle and others brings about a reduction in the weight of the male or female gonads of fowls or pigeons, was without effect in the very young chicks.
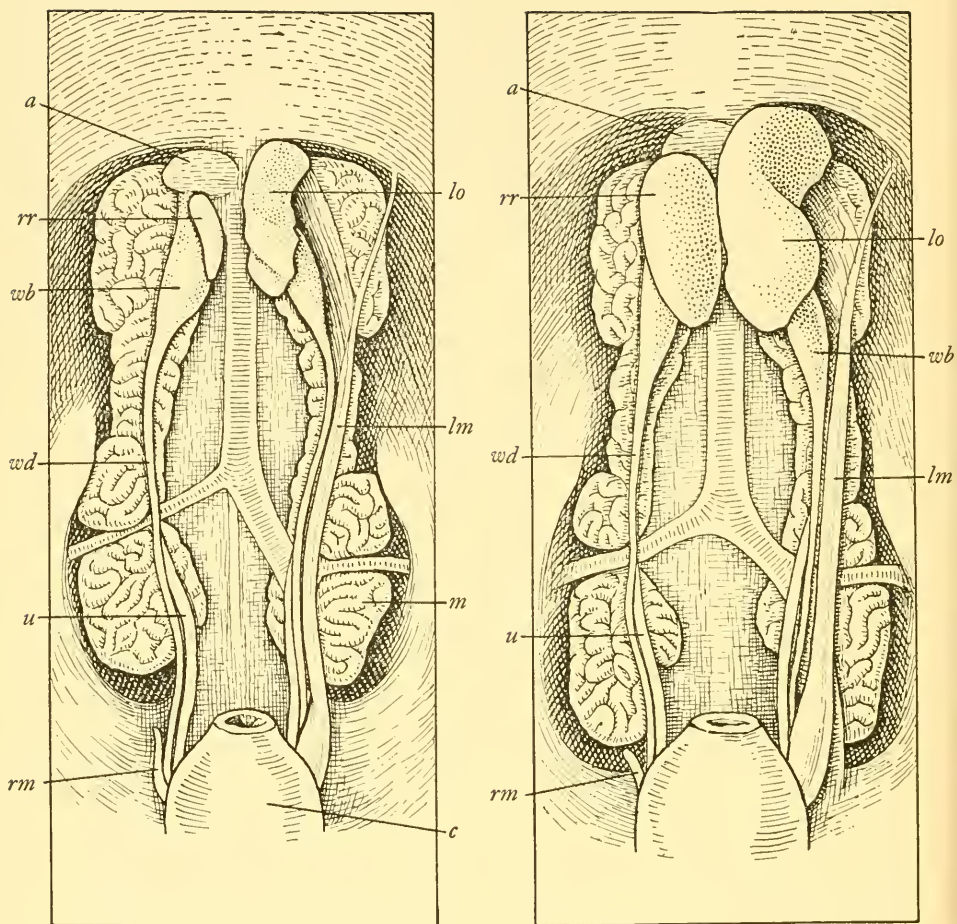
K. Toda '35

FIG. 9.—The action of pituitary gonadotropic hormone on the urogenital tract of the female chick embryo. (From Domm and Dennis, Proc. Soc. Exp. Biol. Med., **36**, 766–69 [1937].)

Left: control; *right:* treated embryo which received 5 rat-units of sheep pituitary extract for 5 days (fifth to ninth day of incubation); incubation of both embryos continued until the eighteenth day. *rr:* right rudimentary gonad; *lo:* left ovary; *wb:* Wolffian body; *wd:* Wolffian duct; *lm:* left Müllerian duct; *rm:* remnant of right Müllerian duct; *a:* adrenal; *c:* cloaca; *m:* kidney; *u:* ureter.

he concluded that the action of follicle-stimulating hormone (of the pig's pituitary) is inhibited if, prior to injection, it has been mixed with luteinizing hormone, lactogenic hormone, or an extract of pregnancy-urine.

Compensatory hypertrophy of the testis as well as several other phases of the pituitary-gonad interrelationship was studied in Leghorn cockerels by Belsky (1936). The author concluded that the compensatory hypertrophy in young birds is associated with pituitary hypertrophy. Under other conditions hypertrophy of the pituitary is associated with an absence or diminution of gonad function (castration or times of seasonal rest of the gonads).

Brown Leghorn hens were hypophysectomized by Hill and Parkes (1935). The expected reversion of the feathers to the male (asexual) type was observed only in the neck hackles. Plumage changes characteristic of thyroidectomy appeared in the hypophysectomized cock. These changes as well as atrophy of the testis and comb could be lessened only for a few days by the injection of beef anterior pituitary extract. The administration of testicular hormone, but not of oestrone, caused growth of the atrophied comb.

Witschi and Keck (1935) investigated the action of extract of the pituitary of the horse and ox on the gonads of the English sparrow. Preliminary observations indicated that great seasonal variations occur in both sexes—marked growth of the gonads occurring in spring and early summer and rapid involution taking place in July and August.[8] Secondary sexual characters such as the color, shape, and texture of the bill underwent corresponding alterations. The daily administration of pituitary gonadotropic hormone (e.g., 2 rat-units for 16–33 days) could cause a sixty-fold increase in the size of the testis or ovary of birds with resting gonads. The anticipated alterations in secondary sexual characters, such as

[8] During involution the testis might regress to one-thousandth its previous size; the ovary might atrophy to the size of that of an immature bird 2–3 months old.

the color of the bill and the size of the oviduct, were observed (see Figs. 10 and 11).

The pituitary of birds contains gonadotropic hormone capable of stimulating the mammalian ovary (Leonard, 1937, fowl pituitary, ovulation in the rabbit, or ovarian hypertrophy in the normal or hypophysectomized rat; Witschi, Stanley, and Riley, 1937, turkey pituitary, ovarian hypertrophy in the normal or hypophysectomized rat). Leonard concluded that the fowl's pituitary contains luteinizing hormone as well as the hormone stimulating the adrenal cortex.
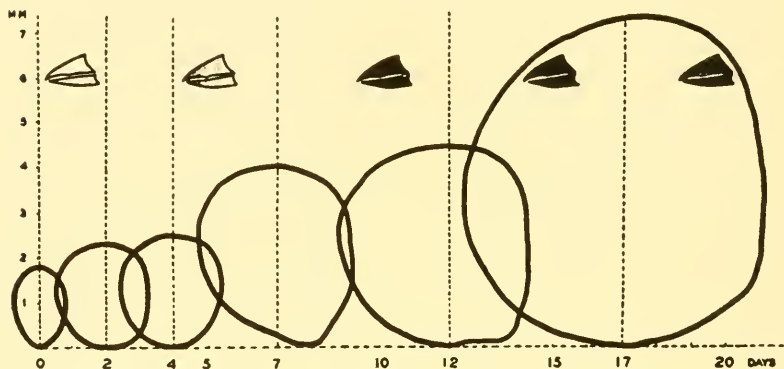
Fig. 10.—The effect of daily injections of 2 rat-units of pituitary gonadotropic hormone on the size of the testis and the color of the bill of the English sparrow. (From Witschi and Keck, Proc. Soc. Exp. Biol. Med., **32**, 598–603 [1935].)

A few other observations were made, chiefly in male birds. Evans and others (1936) concluded that the apparently great sensitivity of the immature pigeon's testis toward pituitary gonadotropic hormone depends upon the lack of effect of pituitary "antagonist." If the latter is first removed from a pituitary extract, the ovary of the immature rat is equally sensitive. Riddle and Schooley (1935), basing their assays on the testicular response of the immature ring dove, studied the gonadotropic potency of the pituitary of the pigeon and the rat. The pituitary of pigeons or ring doves, 1.8–2.5 months after hatching, contained no gonadotropic

(follicle-stimulating) hormone. The pituitary of the adult pigeon was more potent than that of the immature rat. Clark, Leonard, and Bump (1937) reported that the testis of the immature pheasant responds well to the administration of sheep pituitary extract. A study of the changes in the testis and comb of chicks receiving injections of male hormone (extract of male urine, dihydroandrosterone benzoate, testosterone, or its propionate) was made by Breneman (1937). In some instances testicular growth was prevented during

Fig. 11.—The effect of 16 daily injections of 2 rat-units of pituitary gonadotropic hormone on the ovary and oviduct of the English sparrow. (From Witschi and Keck, Proc. Soc. Exp. Biol. Med., **32,** 598–603 [1935].) *Left:* largest of controls; *right:* injected bird.

the period of injection (5–10 day after hatching) but increased markedly during the three following weeks. Bagg (1936) was interested in the production of teratomata in the fowl's testis by injecting into the gland 0.3 cc. of a 5 per cent aqueous solution of $ZnCl_2$. His injection schedules were most varied and his results permit only the following conclusions: (1) previous treatment with sheep pituitary extract made possible the production of teratoma testis in 2 of 26 birds (one in June, the other in August), resembling the effect of zinc chloride solution alone (2 of 20 birds in the spring); (2)

[57]

at seasons other than spring, this effect is not produced by zinc chloride solution (200 birds); (3) although prolan was used, there is no evidence that it had any effect.

The effects of light on the activity of the gonads has received increased attention since 1934.[9] In certain vertebrates in which sexual activity is cyclic, i.e., varies with the season, light-variation appears to be the principal environmental change responsible for the growth or decay of activity of the reproductive organs. It is reasonable to conclude that the stimulus of light reflexly initiates the secretion of gonadotropic hormones by the anterior pituitary.[10] What Bissonnette termed "sexual photo-periodicity" probably depends upon the effect of radiations of different wave-lengths on an opticohypothalamo-hypophysial, nervous glandular mechanism. The most convincing data have been secured in birds and mammals.

According to Hoover (1937), precocious ovulation and spermatogenesis occur in rainbow trout (*Salmo irideus*), if the fish are subjected to prolonged illumination during the period of sexual inactivity. Such trout normally spawn in March (New Hampshire). In brook trout (*Salvelinus fontinalis*) spawning takes place when the hours of daylight are diminishing (October to December). Hoover produced in this species ovulation and spermatogenesis three months earlier than normal by increasing and then diminishing the duration of illumination. In the horned lizard, *Phrynosoma cornutum*, increased light and a higher temperature did not modify the size of the sexual organs during hibernation (Mellish, 1936).

Direct evidence that light may control cyclic sexual activity in birds and mammals is furnished by studies of the morphology of the gonads or of the effects of their internal

[9] For recently published, general articles, see Bissonnette (1936) and Marshall (1937).

[10] Marshall (1937) cited evidence that in a few animals increased activity of the gonads is associated with reduced solar illumination. This also appears to be true of the macaque monkey in captivity.

secretions on behavior or on secondary sexual characters. The inference that these changes represent the effects of a reflex release of anterior pituitary gonadotropic hormones appears to be justified, because (1) the pars glandularis is as necessary for the maintenance of the avian gonads as for the mammalian, (2) the administration of pituitary gonadotropic hormone may markedly stimulate the immature or resting gonads of birds or mammals, (3) in some experiments (in the drake, Benoit, 1936; in the ferret, Bissonnette, 1935) it has been shown that the removal of the pars glandularis prevents gonad-stimulation, otherwise occurring as a result of increased illumination, and (4) the anterior pituitary contains nerve fibers, probably secretory in character, which have a likely origin in hypothalamic nuclei. To Rowan (1925) belongs the credit for making the first experimental observations in birds. He concluded that prolonged artificial illumination of the junco (*Junco hyemalis*) leads to precocious testicular development during the period of sexual inactivity. Recent studies bearing on the effect of light or the mechanism of this effect have been made in game birds[11] and in the sparrow and duck.

In the English sparrow (*Passer domesticus*) the "ration of light" may largely determine testicular growth so that in midwinter increased illumination may cause precocious testicular hypertrophy with spermatogenesis and blackening of the beak. Temperature, as Rowan concluded from his study in the junco, is of little importance. In the spring, however, reduced illumination may partially but not completely suppress normal testicular development (Kirschbaum and Ringoen, 1936). From later studies, the authors (Ringoen and Kirschbaum, 1937) concluded that the testicular response to light depends almost entirely upon a "stimulus through the

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[11] Observations of Clark, Leonard, and Bump (1937) in the grouse, pheasant, and quail. The authors suggested that regression of the gonads in the presence of an apparently adequate photostimulus is due, for unknown reasons, to a lessened anterior pituitary secretion, inasmuch as gonad-stimulation by injected extract can still be produced.

ocular region." In contrast to this view, Ivanowa (1935) believed that an important part of the effect is due to the action of light on the whole body surface. According to Benoit (1935), neither section of the optic nerves nor enucleation of the eyes prevents precocious testicular growth caused by artificial light in the immature drake. Apparently the light had to reach the empty orbits; for if hoods were placed over the latter, testicular development was prevented. Experiments like those just cited indicate the urgent need for more observations on the afferent pathways of reflex photostimulation of the pituitary in birds. Ivanowa's experiments are open to the objection that the birds' eyes may not have been adequately hooded. It is difficult to believe that there is an important peripheral afferent arc other than the optic nerve.

Benoit (1935–37) has made a number of other observations in drakes either immature or during the period of normal regression of the testis. (The effects on the gonad of the female are slight and appear much more slowly.) The testicular response depends not only upon the duration of illumination but also upon the wave-lengths (quality)[12] used and the distribution of "light-dosage." Testicular growth ceases if, during artificial illumination, the drake's anterior pituitary is removed. The gonadotropic potency of the drake's pituitary in immature mice may be increased if the hours of illumination are experimentally lengthened. Such experimental development of the testis and penis, for some weeks at least, was found to be lessened greatly by thyroidectomy. How thyroid deficiency acts, whether by interfering with secretion by the stimulating organ (anterior pituitary) or by diminishing the response of the end organ (testis), is not clear. The feeding of thyroid extract or the injection of thyroxine accelerates the rate of testicular growth.

Light has been shown to influence greatly the development of the gonads or secondary sexual characters including be-

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[12] In one report, Benoit states that red and infrared radiations are especially effective.

havior in mammals with yearly sexual cycles. Oestrus and the conditions necessary for its production by artificial illumination have been repeatedly studied in the ferret.[13] Both the "quantity" and the wave-length of light are important. Variations in duration, the quantity of light remaining unaltered, do not influence the rate of acceleration of oestrus (Marshall and Bowden). These authors also concluded that, whereas infrared rays had little effect, ultraviolet rays caused a premature appearance and abnormal persistence of oestrus. Bissonnette found that the light and hair cycles of the ferret depended upon an intact pituitary. Hypophysectomy prevented both oestrus and its associated hair cycle even in animals artificially illuminated. Apparently the effect on hairgrowth may be due to the direct action of a pituitary hormone, inasmuch as cyclic changes in hair-growth are not influenced by gonadectomy. Hill and Parkes were not able to prevent or delay the onset of oestrus and gonad development at the usual time of breeding by keeping animals in darkness. Although the authors agreed that the effect of light on the anterior pituitary probably explains how oestrus is initiated in the anoestrous season by increased illumination, they denied that the increasing length of daylight is responsible for normal oestrus. Bissonnette stated that the latter may be delayed or made to persist by severing both optic nerves. Ferrets in precocious oestrus have been successfully bred by Bissonnette and Bailey.

In a preliminary report, Whitaker (1936) reported that white-footed mice (*Peromyscus leucopus noveboracensis*) went into oestrus 6–8 weeks early if they were treated with a commercial ultraviolet lamp. By the increase of the daily ration of artificial illumination a similarly precocious oestrus with pregnancy was produced in the raccoon (*Procyon lotor*) by Bissonnette and Csech (1937). In the female rat, reversed illumination (light by night, darkness by day), darkness, or

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[13] Late reports are those of Hill and Parkes (1934), Bissonnette (1935), Bissonnette and Bailey (1936), and Marshall and Bowden (1936).

a constant auditory stimulus does not affect the periodicity of the oestrous cycle (Browman, 1937). However, the author found that constant illumination might cause a persistence of oestrous smears of the vaginal epithelium from a few days to several weeks. Normal cycles of oestrus, as would be expected, were present in animals blinded by cutting the optic nerves or enucleating the eyeballs. Either operation caused a resumption of normal cycles in animals in constant oestrus because of continuous illumination or prevented the development of persistent oestrus in similarly treated animals.[14]

Mammals.—In this section, recently acquired general information concerning the gonadotropic hormones of the pituitary body will be discussed. There will be no further consideration of the effects of light on the secretion of gonadotropic hormones; these are referred to in the preceding section.

1. *Female mammals.*—There is a number of new reports chiefly concerned with the effects of hypophysectomy on the female gonads.[15] Swezy (1936) has again affirmed that the rate of ovogenesis is accelerated in the rat's ovary as a result of hypophysectomy. However, degeneration of the follicle appears after growth has proceeded to a depth of 6–8 rows of cells. She pointed out that this is the sole example of a

[14] See also Hemmingsen and Krarup (1937).

[15] Lacassagne (1935) concluded that the cells of the pars glandularis and other parts are quite insensitive toward radon or X-rays. His experiments were performed in rabbits. Although he was able, by the insertion of a tube containing 1 mg. of radium, to cause destruction of the gland for a distance of 1.5–1.8 mm. accompanied by the characteristic secondary changes in the ovary in about a week, he doubted that radiation of the pituitary has therapeutic possibilities so far as ovarian function is concerned. Even after complete destruction of the pars intermedia and pars neuralis together with destruction of two-thirds of the pars glandularis, ovarian function is not affected. His estimate that adequate anterior pituitary secretion is maintained by one-third of the pars glandularis agrees well with the estimates of Aschner (dog) and Smith (rat).

Newell and Pettit (1935) found that irradiation (X-rays directed toward each temple in small doses for 5 weeks) led to improvement in the subjective symptoms of two-thirds of a group of women with dysmenorrhea (26 patients). Sham irradiation had the same effect in half the proportion of a group with similar symptoms (i.e., in one-third of a group of 15 patients).

biological process undergoing acceleration as a result of anterior pituitary deficiency. Some dilute acid extracts of the pars glandularis produced the same effect—suggesting that
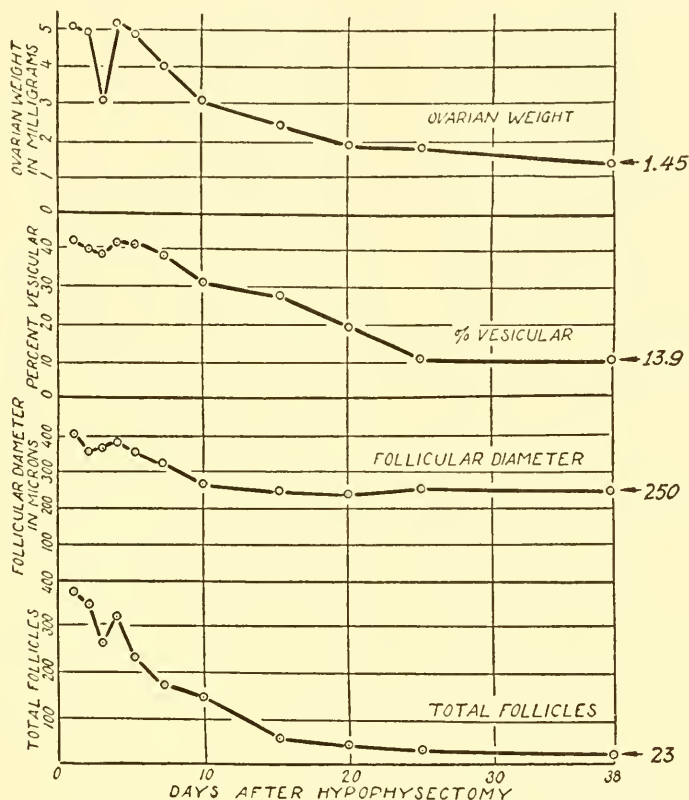

Fig. 12.—Variations in the weight, total follicle-count, mean diameter of the largest follicles, and per cent of vesicular follicles of the ovary of the rat following hypophysectomy at an age of 28 days. Each point represents the mean of determinations from 3 rats. (From Lane and Greep, Anat. Rec., **63**, 139–46 [1935].)

this action was due to inhibition of anterior pituitary secretion. Lane and Greep (1935) studied in detail the follicles and the weight of the ovary of the rat hypophysectomized at an age of 28 days. A graph summarizing their results is reproduced in Figure 12. It will be noted that groups of

animals were studied for more than 6 weeks after hypophysectomy. These results are of interest to everyone employing hypophysectomized immature female rats for the assay of gonadotropic hormone. The belief that a rise in ovarian weight takes place about 4 days postoperatively requires confirmation. The authors found that the injection of follicle-stimulating hormone into hypophysectomized rats caused an increase in the total number of follicles with a decrease in the proportion of those which were vesicular. The proportion of vesicular follicles—without any effect on the total number—was increased by the injection of luteinizing hormone.

Because of the monkey's closer biological relationship to man, the experiments of Smith, Tyndale, and Engle (1936) are of unusual interest. These authors found that marked atresia of follicles, especially of those medium sized or large, followed hypophysectomy in the macaque (*Macaca mulatta*). Involutionary changes in the endometrium and vagina were as great as or greater than those following spaying. Uterine bleeding for 3–6 days occurred 2–4 days after hypophysectomy in the middle of the cycle (stage of follicular growth or proliferation) but was prevented by the daily administration of oestrin. No prolongation of bleeding followed hypophysectomy during menstruation. The usual changes in the uterine mucosa were produced by oestrin or progesterone. Uterine bleeding was delayed but usually followed (8 of 10 monkeys) "oestrin-deprivation"; therefore, the authors' results speak strongly against Hartman's view that such bleeding requires a secretion of the pars neuralis.

In the hypophysectomized and ovariectomized rabbit, the injection of progestin (1 rabbit-unit) neither prevents the motility-increasing effect of oestrone on the uterus nor renders the latter oxytocin-insensitive as in spayed rabbits. To produce these effects in the doubly operated animals, the dose of progestin must be increased to 4 rabbit-units (Reynolds, Firor, and Allen, 1936).

According to Bachman (1936) interstitial stroma may make up a large part of the ovary of the mature rabbit but largely disappears after hypophysectomy.[16] Robson's experiments in the rabbit (1937) illustrate how rapid regressive changes in the ovaries may render the latter almost unresponsive to gonadotropic hormones—i.e., extract of rabbit or horse pituitary or of human pregnancy-urine. A week or more after hypophysectomy, the injection of these hormones had little or no effect on the ovaries, whereas if injections were begun at once, small doses of gonadotropic hormone maintained ovarian function as shown by functional persistence of the corpora lutea of pseudopregnancy (8 days) and by ovulation in response to gonadotropic hormone (12 days). Other experiments led Robson to conclude that both the pituitary and the ovary are essential for maintaining pregnancy in the rabbit. However, he was able to maintain pregnancy in the hypophysectomized rabbit, for some time at least, by injections of progesterone. The rate of atrophy of the corpora lutea apparently was not affected. It appears that among mammals, the mouse and rat are exceptional in that the corpora lutea in the latter part of pregnancy require no pituitary luteinizing hormone for their maintenance.[17]

Emery (1936) reported that homo-implants of the pituitary in the peritoneal cavity or skeletal muscle of rats apparently lived from several days to a week. Often such grafts became vascularized, retained some gonadotropic potency, and appeared nearly normal histologically. Other observations on the secretory capacity of implants or transplants have been made in hypophysectomized mice, rats, and guinea pigs.

[16] The observations of Westman and Jacobsohn (1936) on the effects of hypophysectomy in the rabbit are largely confirmatory of earlier work.

[17] Houssay (1935) has confirmed the finding that hypophysectomy in the pregnant dog is followed by abortion or fetal resorption. He stated that even in late pregnancy abortion might appear in 2 days.

Bellerby (1935) found that the intravenous injection of anterior-lobe extract into pregnant rabbits almost always was followed by abortion or fetal resorption. Ovulation was often produced; hemorrhagic follicles were more frequently produced early or late in pregnancy.

According to Hill and Gardner (1936), successful homo-transplantation of the pituitary into the testis can be made in mice which are homogeneous genetically. They showed that mice carrying such grafts could be hypophysectomized, yet spermatogenesis, normal testicular germinal epithelium, and normal adrenal cortex (at least the zona fasciculata) were all maintained. If both the pituitary and ovary were transplanted, ovarian secretion was elaborated and even caused development of the branched ducts of the mammary gland. Like Hill and Gardner, Greep (1936) found that the sex of the donor of a pituitary transplant had little or no significance. For example, the male reproductive organs were as well maintained by a female pituitary as by a male gland. Greep hypophysectomized male and female rats 4 weeks old. He inserted the graft into the empty sella immediately after operation and was able to secure quite complete replacement effects in three-fourths of the animals. Oestrous cycles in the females were usually a little prolonged (5–7 days) because of a longer dioestrus. However, 13 of the rats became pregnant, delivered normally, and nursed their young. Still another form of replacement-therapy in the hypophysectomized rat was studied by May (1937), who transplanted the pituitary of the new-born rat into the anterior chamber of the eye. Oestrus was first observed 77 days later; there was some increase in weight over a long period (56–119 gm. in 248 days). Oestrus might disappear after removal of the eye containing the transplant, with associated atrophy of the ovary and uterus. Schweizer, Charipper, and Haterius (1937) made ocular transplants (anterior chamber or lateral subconjunctival tissue) of the pituitary in hypophysectomized guinea pigs. After about two months the graft clearly seemed to secrete only one gonadotropic hormone—that stimulating the follicle. This was shown not only by the abnormal development of ovarian follicles and continuous oestrus in the host but also by the effect of implantation of the graft which seemed to produce only follicle-stimulation.

Several observations of general interest should also be mentioned. Lipschütz (1936) reported additional studies in guinea pigs from which about three-fourths of the total ovarian tissue had been removed. If the operation was performed in new-born animals, it produced little disturbance of the development and function of the genital tract owing, the author concluded, to the great reserve of primordial follicles. Sometimes months after the same operation was performed in immature animals (13–28 days old), the vagina remained open for abnormal periods and the uterine changes (cystic hyperplasia of the endometrium, etc.) resembled those of metropathic hemorrhage in man. It is not clear to what extent the responsibility for these changes must be attributed to the ovary or to the anterior pituitary or to both. Hamlett (1935) investigated the effects of whole pituitary extract and prolan ("Antuitrin S") on the genital tract of the armadillo (*Dasypus novemcinctus*). In this animal the blastocyst—i.e., fertilized ovum which has undergone cleavage—lies free in the uterine cavity for four months ("free vesicle period"). Neither hormone hastened implantation; prolan (4 cases) but not pituitary extract (2 cases) caused abortion or resorption of the unimplanted blastocyst. Either hormone was found to cause follicle growth, luteinization, and, occasionally, ovulation. According to Lipschütz and Oviedo (1935), the gonadotropic potency (immature rat) of the pituitary of the ratlike South American mammal *Myocastor* (*Myopotamus*) *coypu* is even lower than that of the female guinea pig despite the animal's size (body-weight as great as 4.5 kg.). Its young, like those of the guinea pig, are well developed when born. Hellbaum's demonstration of differences in the qualitative and quantitative effects of the equine pituitary in the immature rat is of great interest (see Fig. 13). If judgment be based upon ovarian hypertrophy (weight), the concentration of gonadotropic hormone is highest in the pituitary of the aged mare and lowest in that of the stallion, fetus, and colt. The potency of the pituitary of the gelding and

mare (both pregnant and non-pregnant) is high. The qualitative effects, which are illustrated by the reproduced figure, suggest that principally follicle-stimulating hormone is produced by the pituitary of the stallion and of the aged mare and gelding, whereas luteinizing hormone also is secreted by the pituitary of the fetus, colt, young gelding, and adult preg-
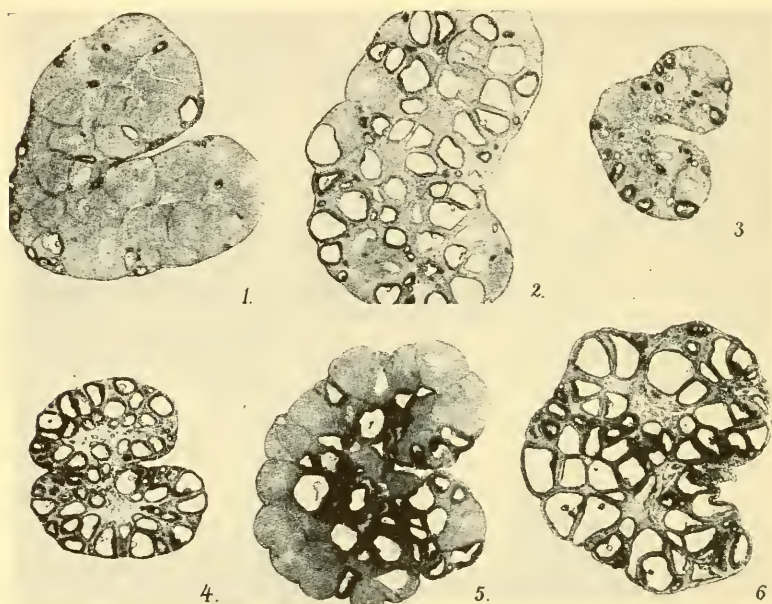

FIG. 13.—Photomicrographs illustrating the response of the ovary of the rat to equal quantities of pituitary powder from glands of horses. The magnifications are the same in all cases. (From Hellbaum, Anat. Rec., **63,** 147–57 [1935].)

1, Normal mare of reproductive age. *2,* Old mare. *3,* Fetus. *4,* Stallion. *5,* Young gelding. *6,* Old gelding.

nant or non-pregnant mare. Those interested in a recent study of the gonadotropic effects of the anterior pituitary of whales (finback, *Balaenoptera physalus;* sperm, *Physeter megalocephalus*) are referred to the report of Geiling (1935).

Cyclic changes in the pituitary in relation to those of the gonads have again been studied by several investigators. Cole and Miller (1935) could detect no change in the gonado-

tropic potency (rabbit-ovulation test) of the ewe's pituitary during this animal's oestrous cycle. Schmidt (1937) found that, as tested in the immature female guinea pig, the gonadotropic potency of the adult female's pituitary is least during oestrus and greatest during pro-oestrus. Also she made a similar study of the pituitary of female adults receiving a minimal sterilizing dose of X-rays. The gonadotropic potency of the pituitary did not always correspond to the normal sexual cycle as judged by the vagina. For example, the pituitary, although removed from an animal in prolonged oestrus, might contain much gonadotropic hormone. The metabolism of the pars glandularis of the rat in different phases of reproductive activity has been investigated by Victor and Andersen (1936) and Andersen, Prest, and Victor (1937). Their results can be summarized as follows:

> Oxygen-consumption:
>   Pro-oestrus > oestrus > dioestrus or spayed
>   Parturition > lactation > pregnancy
> Aerobic glycolysis:
>   Spayed > dioestrus
> Anaerobic glycolysis:
>   Pro-oestrus or oestrus > dioestrus or spayed

The highest oxygen-consumption was found in parturient animals, the lowest in spayed animals. It was about the same in lactating rats and rats in pro-oestrus. There were no significant differences in the aerobic and anaerobic glycolysis of pregnant, parturient, and lactating rats.

The effect of pregnancy on the assay of gonadotropic hormones has been investigated by Rowlands (1935), who used rabbits and expressed dosages in terms of the amount of extract causing ovulation in 50 per cent of each group. Table 1 is a summary of Rowlands' results.

These observations suggest the following conclusions: (1) The "ovulating dose" of a gonadotropic hormone is higher in pregnancy than in oestrus. (2) Pituitary extracts, but not prolan, may vary enormously, depending upon their source,

in their relative gonadotropic potency in rabbits and rats. These observations are not new but are here more accurately confirmed. It is not possible exactly to state how differences are related to the distribution of various pituitary gonadotropic hormones in the extracts. Ox pituitary extract is probably much less potent in follicle-stimulating hormone and richer in luteinizing hormone; perhaps it contains more gonadotropic hormone "antagonist," the effects of which would be more marked in the rat (repeated subcutaneous injections) than in the rabbit (single intravenous injection). The reader is also referred to later discussion (pp. 115–17).

TABLE 1

	RELATIVE DOSE CAUSING			
	Ovulation in 50 Per Cent of Rabbits in			
EXTRACT OF	Oestrus	Pregnancy of Duration of		Ovarian Hypertrophy to 40 Mg. in Immature Rats
		15 Days	25 Days	
Anterior lobe (ox).......	1	2	5	100
Whole pituitary (horse).	20	70	60	100
Pregnancy-urine 1......	25	....	50	100
Pregnancy-urine 2......	20	45	35	100

One other report, unrelated however to pregnancy, may be mentioned here. Bachman (1936) observed that in very young or juvenile rabbits (15–90 days old) the outstanding ovarian change in response to sheep pituitary extract or prolan might be limited to the interstitial stroma in which there appeared large polyhedral cells taking lipoid stains. If, on the other hand, prompt and extensive luteinization of the membrana granulosa occurred, there might be no change in the interstitial tissue. Also, in very young rabbits gonadotropic hormone could cause the formation of corpora lutea without associated progestational changes in the uterus.

According to Morgan (1935), extract of beef anterior lobe or prolan alters the motility of the uterus of the nonanesthe-

tized rabbit according to the predominant change in the ovaries. Increased motility is associated with follicle growth; the change is in the opposite direction, if ovulation and corpus luteum formation occur.[18] Several other possible interrelationships between the uterus and gonadotropic hormones have been studied.[19] Gillard (1937) concluded that hysterectomy in the rabbit delays degeneration of the corpora lutea, thus prolonging pseudopregnancy with hyperemia of the mammary gland. In his experiments, pseudopregnancy lasted about 25 days instead of 18 days in normal animals. Krane's (1937) observations in hysterectomized women, some of whom had been studied as long as 6 years postoperatively, indicated that in the absence of the uterus there may be cyclic excretion of oestrogen, resembling that in normal women, without any increased excretion of gonadotropic hormone. Therefore, hysterectomy is not necessarily associated with a disturbance of the pituitary-gonad interrelationship.

In conclusion, data bearing on the number of gonadotropic hormones or their specific effects will be briefly considered. Loeb and his collaborators,[20] who performed most of their experiments with immature female guinea pigs, describe the following principal gonadotropic effects: (1) the production of follicular atresia or destruction by "atresin," (2) luteinizing effects on the cells of the theca interna or premature luteinization of these cells or maturation of the granulosa of immature follicles, and (3) maturation of the granulosa of large follicles. From a study of the effects of pituitary glands of various animals, of serial implantation, etc., they suggested that these effects might be due to at least three different gonadotropic hormones. More often it is assumed that the

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[18] Morgan found that no effects were produced in spayed rabbits. The earlier work of Reynolds indicated that a reduction of motility is to be expected in normal or spayed rabbits after the injection of beef pituitary extract. However, Reynolds referred to tests made 5–7 hours after injection.

[19] See also Hauptstein and Bühler (1936).

[20] Kunkel and Loeb (1935); Loeb, Saxton, and Hayward (1936); Saxton and Loeb (1937).

important gonadotropic hormones are the follicle-stimulating and luteinizing hormones. Fevold and Hisaw and their co-workers have emphasized that the production of ovulation requires both hormones. Other experiments indicate that the secretion of luteinizing hormone in appropriate amount and at the proper time following follicle growth also is essential for normal oestrus, so that without this hormone, ovulation, mating, corpus luteum formation and maintenance—and hence pregnancy—cannot occur (Casida, 1934; Witschi and Pfeiffer, 1935; Dempsey, Hertz, and Young, 1936). Casida suggested that atretic corpora lutea are due to the administration of an excessive amount of luteinizing hormone. Riddle and others (1936), unable to demonstrate augmentation of the ovulation-producing effect of follicle-stimulating hormone by luteinizing hormone, concluded that the latter is not necessary for ovulation. Inasmuch as their experiments were not performed in hypophysectomized rabbits, this conclusion does not appear to be warranted. The difficulty of the experimental production of ovulation in the oestrous cat was emphasized by Foster and Hisaw (1935), who concluded that at least some luteinizing hormone—even in minute amount relative to the dose of follicle-stimulating hormone—must be administered to cause ovulation. The authors also studied the duration of pseudopregnancy which persisted 40–44 days. In the cats of van Dyke and Li (1938) pseudopregnancy persisted only about 20 days; however, they produced a much smaller number of corpora lutea than did Foster and Hisaw. Van Dyke and Li used prolan also. Experiments in the immature monkey have been described by Hisaw (1935).

Pfeiffer (1937) believed that the male rat pituitary secretes or is able to release much less luteinizing hormone than the female. According to Bunde and Greep (1936), luteinizing hormone or some substance associated with it can cause the rapid regression of corpora lutea in hypophysectomized young adult rats. The earlier experiments of Smith demonstrated how remarkably long the corpora lutea persist after hypophy-

sectomy in the rat. According to Lane and Greep (1935), the effects of separated pituitary hormones in immature hypophysectomized rats are as follows: follicle-stimulating hormone causes an increase in the total number of follicles (numerous small primary follicles) and a decrease in the percentage of vesicular follicles; luteinizing hormone has no action on the total number of follicles but brings about an increase (35–112 per cent) in the proportion of vesicular follicles.

2. *Male mammals.*[21]—A study of the rate of regression of the testes and accessory organs following the removal of the pituitary from 9 guinea pigs has been made by Allanson, Hill, and McPhail (1935). They concluded that maximum atrophy of the testes, epididymides, prostate, and seminal vesicles occurred after about 45 days, although there was marked atrophy of the seminal vesicles after 20–25 days. Atrophy of the secondary sexual organs occurred at about the same rate after castration. According to Leonard and Hamilton (1937), the testis which has been made cryptorchid experimentally degenerates more rapidly (peak at 6 days after operation instead of 10 days), if hypophysectomy is also performed. The authors used rats.

Wells and Moore (1936) found that in the adult or young male ground squirrel (*Citellus tridecemlineatus*),[22] kept in the laboratory, spermatozoa were produced in December and January. Precocious spermatogenesis and full development of the accessory organs were produced weeks or months in advance of the normal time by gonadotropic substances (pitui-

[21] Koch, Schreiber, and Schreiber transplanted pituitary and testis of immature animals into the anterior chamber of the same eye. They observed, in comparison with control experiments, a definite effect on the germinal epithelium. Guinea pigs were used.

Bastenie and Zylberszac (1937) injected an anterior pituitary extract into male or female guinea pigs, which also were given colchicine to arrest the mitoses. There were no striking changes in the gonads. Mitotic division was markedly increased in the epithelium of the seminal vesicles and the uterine mucosa.

[22] Wells and Gomez (1937) describe a technic of hypophysectomy in this animal as well as the effects of the operation in males.
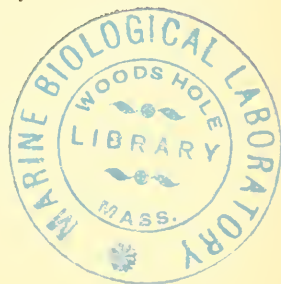
tary implants, prolan, or pregnant-mare serum) or by andro-
gens (androsterone or extract of male urine or bull testis). Why
androgens should have this effect on spermatogenesis is not
known; in view of other work in the rat it is reasonable to be-
lieve that an action on the testicular germinal epithelium is
important. Recent studies of the action of gonadotropic sub-
stances[23] in immature rats have been made by Moore (1936)
and Price (1936). Price compared the effects of pituitary im-
plants and prolan in very young rats. The indirect effect on
the seminal vesicles was accompanied by less change in the
apparent amount of interstitial tissue after pituitary im-
plants than after prolan. Prolonged injection of the latter
caused damage to the germinal epithelium. Moore found
that sheep pituitary and pregnant-mare serum, like prolan,
brought about no precocious spermatogenesis in normal im-
mature rats. The most marked effects were on the inter-
stitial cells and secondary organs; although the seminal vesi-
cles might weigh fifty times as much as those of non-injected
rats, the testicular weight was never more than doubled.
Little change of either type was produced in adult animals.

Follicle-stimulating extract (from the urine after gonad-
ectomy or after the menopause) was injected by Huberman,
Israeloff, and Hymovitz (1937) into men with sterility caused
by an endocrine disturbance (300–2,000 rat-units as 50 rat-
units twice weekly). The treatment appeared to cause an in-
crease in the number and motility of the spermatozoa but
did not correct the sterility.

Using normal rats 21 days old and hypophysectomized rats
35 days old (7 days after hypophysectomy), Greep, Fevold,
and Hisaw (1936) compared the effects on the male reproduc-
tive organs of follicle-stimulating extract and luteinizing ex-
tract made by them from sheep pituitary. They concluded
that the follicle-stimulating extract had no effect on the inter-
stitial tissue but caused increased mitotic division of the cells
of the germinal epithelium so that spermatogenesis could be

[23] Pituitary homo-implants, sheep pituitary, prolan, and pregnant-mare serum.

carried as far as the secondary spermatocyte stage. The luteinizing extract brought about growth of the interstitial tissue but left the germinal epithelium as "degenerate" as in control animals. Increased diameter of the tubules in rats receiving luteinizing extract was believed to be the result of generalized swelling of the tubules partly owing to the accumulation of fluid in the lumen. The administration of a mixture of the two extracts apparently produced an augmented effect on the secondary organs. The general results are in agreement with the views of many authors: a pituitary follicle-stimulating hormone maintains gametogenesis in the male; a pituitary luteinizing hormone is essential for the normal functioning of the interstitial tissue. However, proof to silence all arguments to the contrary awaits the isolation of the hormones in pure form.

Pfeiffer (1936–37) offered experimental evidence that the pituitary of the male rat secretes only follicle-stimulating hormone, whereas the female pituitary secretes both follicle-stimulating and luteinizing hormone. His conclusions are supported by a different type of data—i.e., effects of extracts or implants of the pituitaries of male or female rats—gathered by others. Thus it would appear that follicle-stimulating hormone alone maintains both the germinal epithelium and the interstitial cells of the testis of the normal rat. Greep has suggested that minute continuous secretion of luteinizing hormone (the male rat's pituitary does contain a very small amount of this hormone) by the male pituitary may be sufficient for the needs of the interstitial cells, which probably secrete continuously rather than in a cyclic fashion. The cyclic course of ovarian activity as well as the action of oestrogen on the pituitary might account for the much larger amount of luteinizing hormone secreted by the female pituitary. A later report of Greep and Fevold (1937) further complicates discussion. Follicle-stimulating hormone or luteinizing hormone was administered to adult hypophysectomized male rats. Spermatogenesis could be maintained by either

extract, whereas regression of the interstitial cells was prevented only by luteinizing hormone.

The secretion of gonadotropic hormones in relation to sex and the internal secretions of the gonads. 1. *Differences related to sex and age.*—McQueen-Williams (1935) studied the gonadotropic potency of the pituitary of rats of different ages and sexes. Her data supplement those of Clark previously referred to. McQueen-Williams performed her assays by means of intramuscular implants in immature female rats, whereas Clark used immature mice for assay. Both authors found that the female pituitary is much the more potent in rats about 3 weeks old, whereas in adult rats the male pituitary is richer in gonadotropic hormone. One important change encountered by McQueen-Williams was a remarkable increase in the potency of the pituitary of male rats 27–30 days old, the pituitary then being more potent than at any other age studied. The gonadotropic potency of the pituitary of male rats only a week older was again low and did not rise until the animals were more than four months old.[24] Bates, Riddle, and Lahr (1935) compared the concentrations of gonadotropic hormone in the pituitary of the ox (embryo, calf, adult steer [castrated male], adult bull, normal cow, and cow in early and late pregnancy.) Gonadotropic hormone was determined by its effect on the testis of the immature dove. The authors concluded that the only significant differences were (1) the low potency of the steer's pituitary (concentration about 23 per cent less than the average of others) and (2) the high potency of the pituitary of the cow in early pregnancy (concentration about 36 per cent more than the average of others). The low potency of the steer's pituitary is surprising; also, it might be expected that the pituitary of pregnancy would be poor rather than rich in gonadotropic hormone. In

[24] The pituitaries of rats between the ages of forty-four days and four months were not investigated.

TABLE 2

The Gonadotropic Potency of the Anterior Pituitary in Relation to Sex*

Animal Serving as Donor	Assay Method	Conclusion as to Potency in Terms of			Authority
		Gonado-tropic Hormone	Follicle-Stimu-lating Hormone	Luteinizing Hormone	
Adult frog (*Rana pipiens*)..	Ovulation in frog	♀ > ♂	....	....	Rugh (1937)
Adult salamander (*Triturus viri-descens*)........	Oviposition in *T. viridescens*	♂ ≧ ♀	....	....	Adams and Mayo (1936)
Fowl.............	Hypertrophy of fowl testis	♂ ⋛ ♀	....	....	Domm (1931–33)
Adult guinea pig...	Ovarian effects in immature guinea pig	♂ > ♀	....	....	Schmidt (1937)
Adult guinea pig...	Ovarian change in immature rat	....	....	"Absent" in ♂ and ♀	Lipschütz (1937)
Rat: 27–30 days old............	Ovarian change in immature rat	♂ > ♀	....	....	McQueen-Williams (1935)*
Adult rat.........	Ovarian change in immature rat	....	....	♂ > ♀ ♀̶ > ♀ ♂̶ = ♂†	Lipschütz and Villagran (1937)
Adult rat.........	Appearance of ovarian trans-plant	....	....	♀ > ♂‡ ♂̶ > ♂§	Pfeiffer (1936)
Adult rat.........	Ovarian change in immature rat with or without pro-lan or extract of urine of menopause	....	♀̶ > ♀	....	Leonard (1937)

* See also Table V, p. 143, of earlier volume.

† In terms of concentration. After castration the male pituitary increases in size. Gonadectomized animals are indicated by ♀̶ or ♂̶.

‡ The author believed that the pituitary of the normal male secretes only follicle-stimulating hormone.

§ Castrated at birth.

the guinea pig, the presence of a gonad, functioning definitely but at a low level, appears not to lessen the gonadotropic potency of the pituitary in comparison with that of gonadectomized animals (Lipschütz, 1936).

Other observations on the relation of sex to the pituitary's content of gonadotropic hormone have attempted to distinguish between the follicle-stimulating and luteinizing hormones. According to Lipschütz and Del-Pino (1936), man resembles the rat and guinea pig in that (tested in the immature rat) the male pituitary causes more formation of lutein tissue than the female. (The pituitary of women in the first month of pregnancy caused luteinization of the ovaries; in the later months this effect diminished or disappeared.) The opposite view was expressed by Pfeiffer (1936–37), as well as by others, whose experiments were performed in rats. According to this author, the male pituitary is capable of secreting very little luteinizing hormone. Moreover, Pfeiffer's conclusion appears to be based on a more "physiological" method (the behavior of ovarian grafts as affected by the gonadotropic hormone secreted by the host's pituitary). The conflicting views expressed in recent reports are summarized in Table 2. Some of these results will be considered later when an evaluation will be attempted. Pfeiffer (1936), relying on the effect on ovarian transplants of gonadotropic hormone released by the rat's pituitary *in situ*, concluded that the normal male pituitary secretes follicle-stimulating hormone with little or no luteinizing hormone, whereas the female pituitary is "bipotential"—i.e., secretes both hormones. Also he believed that this sexual difference is hormonal rather than genetic and that after puberty the pattern of pituitary secretion is practically fixed; Pfeiffer (1936–37) cites other experiments in support of these views.

2. *Experiments with animals in parabiosis.*[25]—No attempt

[25] Unless there is a statement to the contrary, all the animals used are rats. References to other experiments employing the method of parabiosis will be found both in this chapter and in the Index. ♀ refers to a normal female; ⚥ refers to a

will be made to recapitulate the older experiments with parabiotic animals; an outline of the results of these experiments will be found in the earlier volume. The outstanding fact previously demonstrated is that, if a gonadectomized and a normal animal are joined in parabiosis, an abnormal stimulation of the gonads occurs and persists for months, because, in all likelihood, abnormal amounts of pituitary gonadotropic hormone are present in the blood. This is particularly true of the experiment ♀ ♂.[26] In the experiment ♂ ♂, the accessory organs of the castrated male remain atrophic. However, according to McCullagh and Walsh (1935), the injection of a comb-growth–stimulating hormone ("androtin") prevents both a gonadotropic effect in the normal male and a regression of the accessory organs in the castrated male.[27] De Mello (1936) placed an ovarian graft in the normal male of the parabiotic pair ♂ ♂. A hypertrophy of the prostate and seminal vesicles of the normal male, abnormal even for such an experiment, apparently was caused by the combined effects of ovarian and testicular secretions. Both the graft and the testes *in situ* were stimulated.

Recently additional observations have been made on the results of parabiosis between hypophysectomized and normal or gonadectomized rats. In experiments of the type ♂ h ♂,

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spayed female; ♂ refers to a normal male; ♂ refers to a castrated male; ♀ h refers to a hypophysectomized female, etc. ♂ h ♂ would refer to a parabiosis between a hypophysectomized male and a castrated male.

[26] In this experiment, the ovaries become cystic and remain in this condition for months. Coincidently, the changes characteristic of oestrus are observed in the uterus and vagina. Evans, Simpson, and Pencharz (1935) suggest that the castrated male pituitary contains (secretes?) but does not release luteinizing hormone. They implanted the pituitary of castrated male rats into female rats hypophysectomized at an age of 26 days. Follicle-stimulation followed the smaller dose of pituitary tissue, whereas corpora lutea were formed after the larger dose (4 glands of young males 40 days after castration). Four glands of normal males caused only follicle-stimulation in accordance with the belief of some authors that the normal male pituitary "releases" only follicle-stimulating hormone.

[27] The authors stated that a specific substance in testicular extract ("inhibin") prevents oestrous cycles in the female rat and causes atrophy of the male accessory organs.

both the germinal epithelium and the interstitial tissue were
stimulated by the gonadotropic hormones of the castrated
rat's pituitary. The effects were much less evident if the
hypophysectomized male rat was joined to a normal rat or a
rat with experimental cryptorchidism (Cutuly and Cutuly,
1937; Cutuly, McCullagh, and Cutuly, 1937). From a study
of the changes in the accessory organs and testes which tend-
ed to be parallel, the authors suggest that the testicle requires
only one gonadotropic hormone, whereas the ovary may re-
quire two. Møller-Christensen (1935) has published a long
report of his experiments with rats in parabiosis. He has ad-
vanced the view that in the experiment ♀ ♀, the pituitary
of the normal rat inhibits the activity of its own ovaries. He
cites the experiment ♀ h ♀ : cystic ovaries without corpora
lutea are found in the hypophysectomized rat; atrophy of
secondary organs in the spayed female is moderate and not
advanced.[28] In the experiment ♀ ♀, of course, the ovaries of
the normal female may become cystic; this change can be
observed more certainly in the experiment ♀ ♂. The pitui-
tary of the normal female of the partners ♀ ♀ or ♀ ♂ under-
goes hypertrophy and contains no gonadotropic hormone
(Møller-Christensen). Another type of parabiosis investi-
gated by the author was that symbolized by ♀ h ♀. Normal
oestrous cycles and normal sexual organs were observed in
the normal rat; the gonads and accessory organs of the hy-
pophysectomized rat underwent atrophy. The interpretation
of all these results, especially in terms of an inhibiting effect
of the pituitary on ovarian function, is a suggestion requiring
more supporting data. The contrary effect—increased re-
lease (and diminished utilization) of gonadotropic hormone by
the pituitary after gonadectomy—still appears to be the best
interpretation of most experiments with parabiotic rats.

    3. *The effects of the internal secretions of the gonads on pitui-*

[28] Oestrus in the spayed partner is observed more frequently in the experiment
♀ h ♀ than in the experiment ♀ ♀ (Møller-Christensen, 1933).

tary function. (a) Hormones of the oestrin group.[29,30]—The effects of hormones of the oestrin group on the secretory performance of the pituitary, aside from their pharmacological interest, are important because they furnish a basis for interpreting the interplay of ovarian and pituitary (gonadotropic) hormones. This is true although only one member of the group (oestradiol) probably is a normal secretion of the ovary. Particularly in the preceding sections, other aspects of this problem have been mentioned. The experimental data about to be taken up here extend our knowledge by other technics. The early experiments of Meyer, Leonard, Hisaw, and Martin (1930, 1932) demonstrated the diminished gonadotropic potency of the pituitary of rats which had received injections of oestrin for 4–10 weeks. The publication of their work was followed by numerous reports of related phenomena, which, as far as recent articles are concerned, now require discussion.

Berkowitz (1937) repeatedly added tablets of "Progynon" (oestrone?) for a long period to the tank water in which he kept immature male guppies (*Lebistes reticulatus*). In size, shape, and color the fish ultimately resembled females. No spermatogenesis appeared. The author believed that the treatment accelerated growth. He was unable to demonstrate that the tablets had any effect on adult male fish. The injection of large doses of oestradiol benzoate into the cock causes regression of the comb and spurs (Zondek, 1936). Bates, Riddle, and Lahr (1937) concluded that testicular atrophy occurs if oestrone be injected into adult male ring doves (40 rat-units per day for 10 days). All these effects, like similar effects in mammals, probably depend upon an interference with the secretion of gonadotropic hormones by the pituitary body. Oestrone is said not to affect the egg-laying performance of the fowl (Unik and Liptschina, 1934).

[29] Particularly oestradiol, oestrone, and oestriol, and their esters.

[30] According to Müller (1937), the dose of oestradiol necessary to produce the vaginal signs of oestrus in the thymectomized or spayed rat is much higher as a result of hypophysectomy. These results are contrary to those of Smith (1932), who used oestrin.

According to Bokslag (1937), a number of hormones[31] reduce the gonadotropic potency of the pituitary of rats of both sexes. However, without critical use, his method of assay is objectionable (indirect effects of implants on the uterus and vagina of immature mice). He believed that gonadotropic activity might be increased following the administration of thyroid extract, but not thyroxine. Other studies in rats have been made by Bühler (1936), Fischer and Engel (1936), Halpern and D'Amour (1936), and Emery (1937). Oestrin was found to cause marked atrophy of the testes sometimes comparable to that in hypophysectomized rats.[32] Halpern and D'Amour again reported on the effect of oestrin on the mammary gland. Robson and Henderson (1936) concluded that the pituitary plays no direct part in bleeding like that occurring before oestrus in the bitch. Oestrone or oestriol produced this effect in the absence of the pituitary.[33] As far as the monkey is concerned, moderate doses of oestrin (1,265–1,390 rat-units during 28–39 days) cause a decrease in the number of large follicles and a slight increase in the rate of follicular atresia. Because of this indirect action of oestrin on the rate of secretion of gonadotropic hormone by the anterior pituitary, the damage to the ovary is unimportant (Allen and Diddle, 1935). Of interest and practical importance to the gynecologist are the experiments which have been performed in women. Frank and Salmon (1935) reported that menopausal symptoms were associated with the excretion of gonadotropic hormones. Both the symptoms

[31] Such as oestrone, oestrone benzoate, progesterone, testosterone, androsterone, prolan, etc.

[32] Shumacker and Lamont (1935) found that the administration of 9 rat-units of oestrone daily for nearly 10 weeks was without effect on the microscopic appearance of the ovary or testis of the rat. Emery's experiments indicated that the secretion of gonadotropic hormone by the young female (130–50 gm.) rat's pituitary is scarcely affected by doses of oestrone as high as 20 rat-units daily for 6 weeks. Halpern and D'Amour injected 5 rat-units daily for 3 weeks followed by 20 rat-units daily for 5 weeks.

[33] Oestrin seemed to reduce the reactivity of the uterus to the oxytocic principle of the pars neuralis. The opposite effect follows the administration of oestrin to other animals such as the rabbit.

and the excretion of gonadotropic hormones disappeared after the administration of oestradiol benzoate (4,000–22,000 rat-units; apparently as many as 4,000 R.U. were administered at one time). Enormous doses of oestradiol benzoate have been administered to women[34] so that the excretion of gonadotropic hormone is prevented and uterine bleeding may appear following treatment (500,000–1,500,000 mouse-units during 20–60 days: Jones and MacGregor, 1936; 200,000 [or more] mouse-units with or without progesterone: Zondek, 1937). According to Zondek (1936), 200,000,–300,000 mouse-units of "follicle-hormone" may delay menstruation 6–70 days. He contended that this treatment prevented the secretion of the pituitary luteinizing hormone so that the development of the corpus luteum was inhibited. Also he believed that the treatment increased the rate of secretion of follicle-stimulating hormone. His results should be compared with those of others who used animals and thus could control their experiments better (*vide infra*).[35]

Other experiments in male animals will be referred to briefly.[36] Clauberg (1936) believed that a single dose of 5,000 mouse-units of "follicle-hormone" to adult male mice increased their sexual activity and fertility, partly by causing an increased liberation of gonadotropic hormone by the pituitary and partly by bringing about a hyperemia of the genital tract. According to Tuchman (1936), the administration of 0.4 mg. of "folliculin benzoate" (or 1 mg. of 1-2-benzpyrene) once weekly for 4 weeks causes a cessation of spermatogenesis and a hypertrophy of interstitial tissue in the male guinea pig. In male animals oestrogens usually bring about regressive changes in the testes, especially in the germinal epithe-

[34] In the menopause or with primary or secondary amenorrhea or with amenorrhea following ovariectomy.

[35] Marx, Catchpole, and McKennon (1936) concluded that the uterus retards the onset of the menopause. For example, the clinical and hormonal disturbances characteristic of the menopause appeared earlier after complete hysterectomy than after supravaginal hysterectomy.

[36] See also p. 81.

lium. However, oestrogens are also known to cause hyper-
trophy of some of the male accessory organs. It is probable
that this is a direct effect, although an indirect action on the
testicular interstitial cells may be a participating cause.

The effect of oestrogens on the secretion of follicle-stimu-
lating and especially luteinizing hormones has interested a
number of recent authors. Usually it has been concluded
that enhanced luteinizing effects or abnormally long persist-
ence of corpora lutea already formed may occur as a result of
the injection of an oestrogen. For example, in the adult
mouse, Clauberg (1936) reported that sterility for as long as
29 days occurred after the injection of one or two large doses
of "follicle-hormone." The sterility was attributed to an ab-
normal persistence and growth of corpora lutea which might
be larger than those of pregnancy. In the rat, ovarian hyper-
trophy following the injection of various oestrogens is due to
corpora lutea (Ellison and Burch, 1936; Mazer, Israel, and
Alpers, 1936). Ellison and Burch found that this effect could
be prevented by hypophysectomy. The same conclusion was
reached by Fevold, Hisaw, and Greep (1936) as well as Hohl-
weg and Chamorro (1937), so that it appears that oestrogens
increase the rate of secretion of luteinizing hormone by the
pituitary body.[37] Hohlweg and Chamorro injected 11γ of
oestradiol benzoate into immature female rats; the customary
appearance of corpora lutea after this treatment could be pre-
vented by hypophysectomy on the second day after injection
but not if operation was delayed to the fourth day.

The experiments of Fevold, Hisaw, and Greep were de-
signed to detect changes due to injected oestrin, in the
amounts of follicle-stimulating or luteinizing hormone liber-
ated by the pituitary . After the injection of oestrin (0.1–4
R.U.), a constant dose of pituitary follicle-stimulating hor-
mone was administered. The increased ovarian weight, in
comparison with immature animals receiving no oestrin, was

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[37] Lipschütz has again reported that oestrogens lower the luteinizing potency of
the adult male rat's pituitary (e.g., see Lipschütz, Palacios, and Akel, 1936).

considered to be due to the luteinizing hormone liberated by the pituitary *in situ* and to some extent was related to the size of the oestrin dose.[38] No such increased effect of follicle-stimulating hormone after oestrin occurred in hypophysectomized rats. In normal animals, the injection of prolan after oestrin produced no ovarian hypertrophy greater than after prolan alone. If prolan be considered a luteinizing hormone, this result indicates that oestrin does not facilitate the secretion of a synergizing, follicle-stimulating hormone. If oestrin was injected for 8 days, the ovarian response to pituitary follicle-stimulating hormone or prolan was reduced in normal but not in hypophysectomized rats, indicating that this antagonistic effect is on the pituitary, by which some gonadotropic hormone is secreted even in immature animals, and not on the ovary. All these results suggest the following conclusions: (1) oestrin in small doses increases the rate of secretion of luteinizing, but not of follicle-stimulating, hormone; (2) larger doses of oestrin (8-day injection period) diminish the rate of secretion of both gonadotropic hormones; and (3) oestrin appears to have no effect on the ovary.[39]

Leonard's results (1937) led to a different interpretation as far as conclusion (2) is concerned; however, he used a different method. He estimated the quantity of follicle-stimulating or luteinizing hormone in the pituitary of the rat receiving oestrin by determining the effect of a maximum dose of prolan (50 rat-units) or menopausal urine (equivalent to 100 cc.) and comparing these effects (1) with those of pituitary tissue from control animals and animals receiving oestrin and (2) with the effects of pituitary tissue in addition to prolan or extract of menopausal urine. The degree of augmentation of the effect of prolan on the ovary was taken as a measure of the quantity of follicle-stimulating hormone present in the ad-

[38] The maximum effect apparently was produced by 0.5 R.U. of oestrin.

[39] Earlier work had indicated that ovarian regression due to a "sex hormone" is an indirect result of diminished pituitary function. See, however, the results of Robson in the rabbit discussed on pp. 86–87.

ministered pituitary tissue, whereas similar augmentation of the action of extract of menopausal urine indicated the amount of luteinizing hormone administered. The author administered 10 rat-units of oestrin daily for 10 days. Pituitary tissue in a constant dose of 3.5 mg. dissolved in 0.1 per cent NaOH was always given, so that the results refer to the concentration of a particular gonadotropic hormone. The administration of oestrin to adult, spayed female rats brought about a reduction in the concentration both of follicle-stimulating hormone and of luteinizing hormone.[40] Contrary to the results of Fevold, Hisaw, and Greep, repeated injections of oestrin into immature rats had no effect on the concentration of follicle-stimulating hormone present; however, Leonard agreed that the amount of luteinizing hormone was reduced. It must be remembered that the pituitary body was intact in the immature rats used by Leonard for assay—perhaps constituting a further complicating variable.

Allen and Heckel (1936) reported that pseudopregnancy in the rabbit can be prolonged to 25 days after a sterile mating, provided that oestrin be injected; the authors gave no data on the dosage used. Hidaka (1937) produced pseudopregnancy in rabbits by injecting pregnancy-urine; large doses of an oestrogen caused a prolongation of the condition (5,000–10,000 international units of "Gynandol benzoate" on alternate days). Klaften (1937) injected various doses of oestrone (sometimes as much as 1,200,000 I.U.) to produce corpora lutea. No corpora lueta could be observed in infantile or juvenile rabbits (doses as high as 150,000 I.U.).[41] In adult rabbits there was found, in addition to corpora lutea, glandular cystic hyperplasia of the uterus with loss of sensitivity to the oxytocic principle of the pars neuralis. Robson's results (1937) raise the question of the site of action of an

[40] Castration alone caused a marked increase in the concentration of follicle-stimulating hormone (comparison with normal animals).

[41] Mazer, Israel, and Alpers (1936) stated that mature ovarian follicles could be produced by the injection of large doses of oestrogens into immature rabbits.

oestrogen in causing persistence of corpora lutea. The other evidence available indicates that the secretion of luteinizing hormone by the pars glandularis is responsible for the appearance of corpora lutea, when these follow the injection of an oestrogen. According to Robson, oestrone (10γ daily) or oestradiol (5γ daily) maintains the structure and function of pseudopregnant corpora lutea of hypophysectomized rabbits for as long as 13 days.[42] As in hypophysectomized rabbits receiving no oestrogen, the ovary of these animals did not respond to gonadotropic hormone. The observations of Westman and Jacobsohn (1937) are fully in agreement with those of Robson.

Late in pregnancy in the rat, the administration of 0.5 mg. of oestrone daily increases the duration of pregnancy to about 24–26 days (Selye, Collip, and Thomson, 1935). The authors concluded that this treatment prolongs the life of the corpora lutea, giving rise to interference with parturition and fetal death. Pincus and Kirsch (1936) studied the effect of oestrogens on ovulation and implantation in the rabbit. As much as 3,000 rat-units of oestrone, given before mating, did not prevent ovulation. The administration of oestrone during the 3–6 days after coitus caused a considerable reduction in the number of implantation sites. The authors concluded that ova were killed in the early blastocyst stage but that cleavage was not affected. Some oestrogens were more harmful than others. Implanted ova, like the fetuses into which they developed, were normal. The experiments of Courrier and Gros (1935) in the cat indicated that "folliculin" prevents nidation in the cat if a total dose of 500–1,000 rat-units be administered on the 5–18 days following coitus. Abortion was caused by 1,000 rat-units during the 38–43 days, although other doses at other times might not have this effect.

Experiments in parabiotic rats indicate that oestrone interferes with the liberation of gonadotropic hormone by the gonadectomized partner. Meyer and Hertz (1937) injected

[42] In one experiment 1 mg. of testosterone daily was without effect.

0.05–5.00γ of oestrone daily into the gonadectomized part-
ners of the pairs ♀ ⚥ and ♀ ♂.[43] Rats 30–33 days old were
used and received injections for 11 days. The spayed female
appeared to be more sensitive than the castrated male (e.g.,
weight of both ovaries of ♀ of ♀ ⚥ without injection, 71.0
mg.; similar weight, ♀ of ♀ ⚥, if ⚥ received oestrone, 24.0
mg.). This would be expected from the fact that ovarian
changes are usually more pronounced in the female of the
pair ♀ ♂. Also the authors concluded that by the technic
of parabiosis, a castration change in pituitary function is re-
vealed earlier than by studies of pituitary histology.

According to Victor and Andersen (1937), oestrone or oestra-
diol causes a significant increase in the oxygen-consumption
of the pituitary of the rat, whether the hormone be added to
the surviving pituitary *in vitro* or administered to the spayed
rat about 6 hours before the gland is removed. No such
phenomenon was observed in control tissues (liver, kidney).

b) Progesterone.[44]—Progesterone, like oestrone and andros-
terone, may cause regression of the testes in adult ring doves
(Bates, Riddle, and Lahr, 1937). To obtain this effect the
authors injected 0.25 Clauberg-unit each day for 10 days.

According to Hohlweg (1935) the characteristic effects of
gonadectomy on the pituitary are not corrected by the in-
jection of progesterone, despite reports to the contrary.
Hohlweg found that the administration of 0.54 mg. of pro-
gesterone daily for two weeks to adult spayed rats did not
alter the histologic changes in the pars glandularis. He at-
tributed the positive results of other investigators to con-
tamination of their extracts with an oestrogen or an andro-
gen. Large doses of progesterone inhibit oestrus in the rat
(Selye, Browne, and Collip, 1936; Phillips, 1937). Associated
with this effect are moderate ovarian atrophy and some pitui-

[43] For the meaning of the symbols, see pp. 78–79, n. 25.

[44] Zwarenstein (1937) concluded that progesterone causes ovulation in the toad
(*Xenopus laevis*) by its direct action on the ovary. Shapiro previously had found
that testosterone, androsterone, or certain derivatives of these, adrenal cortical
extract, etc., can cause ovulation in this amphibian.

tary hypertrophy. There is little basis for interpreting these observations, although Bokslag believed that progesterone, like many other substances, lessens the gonadotropic potency of the pituitary. Moreover, Laroche, Simmonet, and Bompard (1937) found that progesterone[45] lessens the urinary excretion of gonadotropic hormone in spayed women or women past the menopause and concluded that its effect therefore resembles that of oestrone. The corpus luteum hormone appears not to affect the testis or secondary sexual organs of immature male rats (Fels, 1936). Fels, however, injected small doses of progesterone (1.2–1.7 mg. as the total dose during 11–22 days).

A few observations in other animals require mention. Dempsey (1937) reported that preovulatory swelling and ovulation are prevented in the guinea pig by the administration of progesterone (0.05 I.U. daily for 20 days). Follicular growth was not inhibited by the hormone. In the rabbit, also, the injection of progesterone prevents ovulation after coitus, although it appears not to diminish the ovulation-producing effect of prolan[46] (Makepeace, Weinstein, and Friedman, 1936–37). These observations extend and confirm earlier reports such as that of Mahnert.

c) Androgenic substances such as hormones extracted from the testes or urine or derivatives of these.[47]—Breneman (1937) studied the effects of androgens on the chick receiving injections between the fifth and tenth days after hatching. Observations were continued to an age of 30 days. Substances such as testosterone or dihydroandrosterone benzoate prevented testicular growth during the injection period. However, three weeks after injections were stopped, the testes weighed almost twice as much as those of non-injected chicks. The author also concluded that dihydroandrosterone ben-

[45] Total doses of 25–58 mg. of progesterone as 5–23 injections over 11–144 days.

[46] In pregnant does, the dose of prolan or extract of the pars glandularis required to produce ovulation is larger than in oestrous rabbits.

[47] Testosterone or androstenedione can cause ovulation by acting on the excised ovary of the toad, *X. laevis* (Shapiro and Zwarenstein, 1937).

zoate potentiates the response of the chick's testis to sheep pituitary extract.

Observations like those of Breneman illustrate the complexity and difficulty of interpreting the reported effects of "sex" hormones on the gonadotropic phase of pituitary function. It is necessary to take into account depressant (and perhaps excitatory) effects[48] on the secretion of gonadotropic hormones as well as substitution-effects on the gonad itself after the removal of the pituitary. For some years the view that "male sex hormone" may lessen the secretion of gonadotropic hormone and thus bring about testicular or ovarian damage has been accepted and can again be illustrated by recent observations in rats. Oestrus, as judged by the vaginal smear, may be prevented in the adult female rat by large doses[49] of several androgens such as testosterone, androsterone,[50] androstanedione, and androstenedione (Browman, 1937; Nelson and Merckel, 1937). Androgens may completely prevent ovarian hypertrophy in the female of the parabionts ♀ ♂, if administered to the castrated male (Hertz and Meyer 1937). The inhibitory effect of three androgens corresponded to their potency as "male hormones" (e.g., testosterone propionate > testosterone > dehydroandrosterone). Hain (1937) concluded that testosterone propionate antagonizes the oestrogenic effect of oestrone in the spayed rat—a conclusion not in accord with the usual view that antagonism of the secretion of the intact ovary by a male hormone is the indirect result of depression of pituitary function. Hain also found that large doses of androgens such as testosterone or its propionate, and transandrostenediol cause abortion in the rat

[48] Pfeiffer's results led to the conclusion that the normal internal secretion of the rat's testis prevents or inhibits the liberation of luteinizing hormone by the pars glandularis.

[49] 0.5–5 mg. daily. Nelson and Merckel usually injected 0.5–1.5 mg. daily for as long as 30 days.

[50] According to Bühler (1936) crystalline "Proviron" (androsterone?) does not inhibit the growth of the uterus and ovaries of immature rats receiving 30–50 capon-units in 8 days.

if injected during midpregnancy or late pregnancy. Oestrone caused the same effect in 0.003 the dose (or less) of androgen required. Recently, Moore and Price (1937) studied the effect of androsterone on the testes and on the gonadotropic potency of the pituitary of young rats. The daily injection of 0.5–1.5 mg. of the androgen for 20 days inhibited testicular growth 12–50 per cent and reduced the gonadotropic action of the injected rat's pituitary. There was no stimulation of spermatogenesis. The authors concluded that the testicular damage was the indirect result of pituitary injury. On the other hand, enormous doses of androsterone (4–6 mg. daily for 20 days) appeared not to affect the testes of adult rats.

It will be recalled that the gonadotropic potency of pituitary implants increases after gonadectomy. Therefore, the normal internal secretions of the ovary or testis appear to inhibit the secretion (storage) of gonadotropic hormone. Clark had earlier found that, judged by the gonad-stimulating effect of pituitary implants, secretion of testicular hormone occurs much earlier than secretion of ovarian hormone in the rat. In other words, castration at an early age is followed by an increased gonadotropic effect of the pituitary, whereas spaying produces no change. Stein (1935) has shown by this technic that there is considerable testicular secretion even in the first week of the male rat's life. A confusing exception to the generalization that gonadectomy is followed by increased storage or secretion of gonadotropic hormone is that reported by Bates, Riddle, and Lahr (1935). They found that the concentration of gonadotropic hormone in the pituitary of the ox, as indicated by testicular hypertrophy in immature doves, is lowest in the castrated animal (adult steer), apparently being lower than in the pituitary of the bull, calf, embryo, etc.

Another aspect of the problem which can be interpreted as indicating an inhibiting effect of androgens on pituitary gonadotropic function is the prevention or correction of castration changes in the pars glandularis. This has been ac-

[91]

complished in castrated male rats by injecting androsterone (Hohlweg, 1937) and in spayed females by injecting androsterone as well as dehydroandrosterone, androstanedione, or testosterone (Nelson and Merckel, 1937). All the authors injected large doses of the androgens used. Schoeller, Dohrn, and Hohlweg (1936) compared the doses of oestradiol benzoate, androsterone, testosterone, and testosterone propionate needed to correct gonadectomy changes in the pituitary of immature or young adult castrated or spayed rats. Oestradiol benzoate (total dose 0.15–0.3γ) was 200–500 times as potent as the androgens in immature animals, whereas in young adult gonadectomized animals of both sexes its potency was 500–13,000 times greater. In the older animals at least, testosterone propionate (total dose 150γ) was found to be the most potent of the androgens, its activity being twice that of testosterone and 10–13 times that of androsterone. Frank and Salmon (1936) found that androgens affected symptoms due to castration only slightly and did not influence the excretion of gonadotropic hormone. Their experiments were performed in two castrated men who received total doses of androgens such as 20 mg. of androsterone, 25 mg. of dihydroandrosterone benzoate, or 115 mg. of testosterone. Apparently androgens are much less potent than oestrogens in correcting pituitary castration changes, whether reference is made to altered morphology or to the storage or rate of secretion of gonadotropic hormones. Salmon's report (1937) also supports this belief. The injection of 815 mg. of testosterone propionate over a period of about 4 weeks into a spayed woman produced effects —i.e., amelioration of menopausal symptoms, disappearance of gonadotropic hormone in urine—corresponding to those of approximately 4 mg. of oestradiol benzoate.

Androgens may cause oestrus, prolonged or only lengthened periodically, in animals with intact ovaries (Nelson and Merckel, 1937). Hypophysectomy seemed to increase this effect of dehydroandrosterone. Hohlweg (1937) believed that

corpus luteum formation may result from the injection of dehydroandrosterone or testosterone into rats. Obviously suppression of oestrus by an androgen might be related to such an action. There is no evidence that the anterior pituitary plays an important part in these effects of androgens. It has been suggested that the ovary may convert an androgen into an oestrogen.

There is good evidence from recently published reports that androgenic substances also directly affect the testes.[51] Wells and Moore (1936) found that androsterone or extract of male urine or bull testis (like gonadotropic extracts) might cause precocious spermatogenesis in the ground squirrel (*Citellus tridecemlineatus*) weeks or months before the germinal epithelium normally becomes active. None of their animals was hypophysectomized. Confirming the work of Walsh, Cuyler, and McCullagh, Nelson and Gallagher (1936) as well as Nelson and Merckel (1937) concluded that "male hormone" (extract of urine, crystalline androgens) maintains spermatogenesis in the hypophysectomized rat.[52] Injection must be started a day or two after hypophysectomy; if there is an interval of 3 weeks between hypophysectomy and initiation of treatment, spermatogenesis cannot be initiated perhaps because of irreparable damage to the germinal epithelium. The treatment does not correct the degenerative changes in the interstitial cells. Cutuly, McCullagh, and Cutuly (1937) believed that the maintenance of scrotal function accounted for the favorable action of androgens on spermatogenesis; however, Nelson and Merckel pointed out that scrotal function

[51] For studies comparing the effect of several androgens on the secondary sexual organs of normal and hypophysectomized male rats, see Freud (1935) and Laqueur, Dingemanse, and Freud (1935). For example, although (with a cosubstance) testosterone and dihydroandrosterone might produce typical responses in hypophysectomized animals, androsterone was almost without action.

[52] McEuen, Selye, and Collip (1937) concluded that normal testicular structure in the hypophysectomized rat is not maintained by the injection of testosterone. Cutuly, McCullagh, and Cutuly (1937) prevented testicular atrophy in hypophysectomized rats by androsterone (1.50 mg. daily) and testosterone (0.45–1.50 mg. daily) but not by dihydroandrosterone benzoate (1.25 mg. daily).

but not spermatogenesis may persist in hypophysectomized rats after the injection of oestrone (1,000 I.U. daily). The fact that certain androgenic substances maintain spermatogenesis in hypophysectomized rats suggests that the normal pituitary gonadotropic hormone necessary for the testis is only that stimulating the interstitial cells. If pituitary secretion insures normal function on the part of the interstitial cells, perhaps the secretion of the latter is all that is needed to maintain spermatogenesis.

The interrelationship between the secretion of gonadotropic hormones and the internal secretions of other glands. 1. The thyroid gland.—Reports published after those previously reviewed still indicate that only exceptionally does there appear to be an important interrelationship between the secretion of gonadotropic hormones and that of the thyroid gland. Gonadectomy in the guinea pig may be followed by moderate proliferative changes in the thyroid according to Kippen and Loeb (1936). Several authors have studied the effect of thyroidectomy on the gonads or their response to gonadotropic hormone. Leonard and Leonard (1937) found that thyroid deficiency of about one week's duration probably had no effect on the number of follicles (including vesicular follicles) of the immature rat's ovary. According to Friedgood and Cannon (1936), a marked maturation of the ova in the rabbit's ovary can be observed several weeks after thyroidectomy. Another aspect of the problem is the testing of the ovarian response to gonadotropic hormones after thyroidectomy.[53] Leonard (1936) tested pituitary or urinary extracts in thyroidectomized or normal rats. The extracts themselves were free from thyrotropic hormone. He concluded that the follicle-stimulating phase of the response is greater in thyroidectomized animals and that thyroid hormone inhibits the action of follicle-stimulating hormone but not that of luteiniz-

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[53] Benoit (1936) observed that the response of the testes and secondary sexual organs of the drake to intensive illumination—probably by an indirect neurohumoral mechanism involving the optic nerves and the pars glandularis—could be prevented by thyroidectomy.

ing gonadotropic hormones such as prolan or pregnant-mare serum.[54] The observations of Tyndale and Levin (1937) support Leonard's conclusions. These authors found that the ovarian response to follicle-stimulating hormone (extract of "menopause urine") may be much greater in hypophysectomized than in normal immature rats. Inasmuch as the injection of thyroxine reduced the ovarian response of similarly treated hypophysectomized rats, they concluded that poor function on the part of the thyroid may account for the difference found. Obviously this suggestion does not exhaust the list of possible explanations. Thyroid hormone probably produces an inhibitory effect by its action on the ovary (see also Fischer and Engel, 1936). On the other hand, the results of Morrin and Loeb (1935) indicated that the response of the guinea pig's ovary to implants of the pars glandularis (guinea pig, ox, rabbit, and rat) was the same whether or not the thyroid had been removed previously.

Halpern and Hendryson (1935) reported that dinitrophenol, a general stimulant of metabolism, does not significantly affect the oestrous cycles of rats and that changes in the oestrous cycles caused by thyroid extract therefore cannot be attributed to the stimulating effect of the extract on metabolism.

2. *The adrenal glands.*—The hormonal variables requiring attention in a consideration of the interrelationship of the pituitary (gonadotropic function) and adrenal glands are pituitary gonadotropic hormones, adrenal cortical stimulating hormone, and the internal secretions of both the gonads and the adrenal cortex.[55] Moreover, the internal secretions of the "end-organs," the gonads and the adrenal cortex, are probably so similar in structure that, under suitable conditions,

[54] Loeb, Saxton, and Hayward (1936) believed that thyrotropic hormone usually is associated with luteinizing hormone and "atresin" in the pituitary. The concentration of follicle-stimulating hormone tends to be low if that of the other three substances is high.

[55] Epinephrine, the important medullary secretion, appears to require no consideration.

they may possess substitutional properties. For example, it appears that the internal secretion of the corpus luteum, progesterone, may be a much less potent but fairly satisfactory substitute for adrenal cortical hormone after adrenalectomy. Therefore, experiments dealing with the interplay of so many variables, to which are added the necessary inaccuracies of biological work, must be interpreted with reserve.

Complete adrenalectomy may affect adversely sexual and, presumably, pituitary gonadotropic function. Until there is better evidence to the contrary, these actions are best interpreted as resulting from the general, nonspecific, harmful effects of a deficiency of the adrenal cortical hormone. Martin and Fazekas (1937) concluded that salt therapy of bilaterally adrenalectomized adult female rats facilitated the normal cyclic sexual phenomena (normal oestrous cycles in 55 per cent of animals receiving salt solution in comparison with normal cycles in 21 per cent of control animals observed for a much shorter period). What observations they made with pituitary implants are not of much value as an aid in interpretation. According to Fitzhugh (1937), adrenalectomy in the rat is followed by a disappearance of oestrous cycles in the female or atrophy and degenerative changes in the testes of the male; he reported that both of these changes could be corrected by the injection of adrenal cortical extract. Britton and Kline (1936) concluded that in the presence of adrenal insufficiency the female rat is usually sterile; if adrenal insufficiency is produced in pregnant animals, abortion commonly occurs and there is no lactation. All these harmful changes can be prevented by adrenal cortical extract. Fertility also is reduced in the adrenalectomized male rat surviving because of accessory tissue. Friedgood (1937) studied the effect of adrenalectomy on ovulation in the cat following coitus. He found that removal of the second adrenal 15–55 minutes after mating was not followed by ovulation (9 cats), whereas if the operation was delayed until 6 hours after mating, normal ovulation occurred (3 cats). Bilateral adrenal-

ectomy did not prevent ovulation due to injected pituitary gonadotropic hormones; however, there appeared to be a retardation of ovulation and interference with the subsequent formation of corpora lutea (Friedgood and Foster, 1937).

Pituitary implants may markedly prolong the life of adrenalectomized young female rats. It is likely that this effect is due to an indirect action on the ovaries: luteinization with abnormal production of corpus luteum hormone occurs (Emery and Schwabe, 1936; Cavanaugh and Gaunt, 1937).[56]

Several authors have declared that extract of the adrenal glands can cause a moderate gonadotropic effect in rats.[57] Extract of the adrenal of the gelding or ox in a dose equivalent to 114 mg. of dried gland was found by Deanesly (1935) to cause oestrous changes in the uterus and enlarged or cystic follicles in the ovaries of 3 of 10 immature rats. The experiments of Allen and Bourne (1936) are of little significance because their female rats were 56–70 days old when used. Fitzhugh (1937) believed that extract containing adrenal cortical hormone causes a slight hypertrophy of the ovaries and uterus or a moderate atrophy of the testes of rats. In the female rat the results were obtained by injecting extract on the 21–44 days of life. Hoffmann (1937) concluded that cortical extracts containing no cortical hormone cause a gonadotropic effect or a potentiation of the action of prolan in immature rats. The maximum effect appeared after 65 hours; the dose used was equivalent to 600 mg. of dried adrenal cortex; the substance responsible for the effect was insoluble in lipoid solvents. Perhaps these effects, elicited with difficulty, are due to an action on the pars glandularis. Corey (1937) was un-

[56] Swingle and others (1937) showed that anterior pituitary extract may prolong the life of bilaterally adrenalectomized cats independently of sex or the gonads. Also they found that the bitch during pseudopregnancy requires no adrenal cortical hormone, although bilaterally adrenalectomized. Their negative results with progesterone in cats were perhaps due to insufficiently large doses.

[57] The secondary sexual organs of castrated, hypophysectomized rats may respond to adrenal cortical stimulating hormone by a stimulation of growth (Davidson, 1937).

able to produce oestrus by injecting potent cortical adrenal extract into adult hypophysectomized female rats.

3. *The epiphysis.*—Despite Engel's statement to the contrary (review, 1936), there is not yet satisfactory evidence that pineal secretion antagonizes the gonadotropic secretion of the pars glandularis. Recent observations are those of Fleischmann and Goldhammer (1936), Tarkhan (1937), and Wade (1937). Wade also used prolan and pregnant-mare serum as gonadotropic substances.

4. *The lactogenic hormone of the anterior pituitary.*[58, 59]— Lactogenic extracts of the pars glandularis, injected into female rats, may cause a prolonged period of dioestrus (Dresel, 1935). Similar results were obtained by Nathanson, Fevold, and Jennison (1937) both with pituitary extract and with an extract of the urine of lactating women. They suggest that luteinizing hormone rather than lactogenic hormone is responsible for the effect. According to Engelhart (1936), the lactogenic hormone brings about extensive luteinization of the rabbit's ovary. However, not all his extracts were free of gonadotropic hormone. Lahr and Riddle (1936) injected lactogenic extract into rats and caused a temporary suppression of oestrous cycles in adult females. Large ovaries containing corpora lutea were present after 8–12 days' treatment. The authors doubted that progesterone-secretion was responsible for the disappearance of oestrous cycles and suggested that either an alteration of ovarian function or an interference with the liberation of follicle-stimulating hormone accounted for the change produced. Desclin and Grégoire (1937) transplanted ovaries to the kidneys of female rats spayed a few days postpartum. Lactation was permitted to continue in half of the group. A comparison of the ovaries of the lactating and nonlactating groups 15 days later led the

[58] Leblond and Nelson (1936) concluded that the maternal instinct depends neither on lactation nor on internal secretions of the anterior pituitary, although these may reinforce or reduce manifestations of the instinct.

[59] See also chap. v.

authors to conclude that the secretion of gonadotropic hormone is inhibited during lactation. According to De Fremery and Denekamp (1935), doses of pituitary lactogenic hormone, large enough to initiate the secretion of milk, cause abortion or fetal death *in utero* if administered to pregnant goats, guinea pigs, rabbits, or rats. The lactogenic extract, prolactin, of Bates, Riddle, and Lahr (1937) caused as marked a regression of the testes of adult pigeons as hypophysectomy. They believed that the extract did not affect the testes but interfered with the liberation (or formation?) of "follicle-stimulating" (gonadotropic) hormone.

The statements in the foregoing paragraph can soon be tested accurately, inasmuch as the isolation of crystalline, lactogenic hormone has been announced recently by White, Catchpole, and Long (1937).

The nervous control of the secretion of gonadotropic hormones. —In the discussion of the effect of light and related radiations on the gonads it was emphasized that many of the observations indicate that the secretion of gonadotropic hormones by the pars glandularis may be reflexly stimulated, the afferent arc being the optic nerves carrying impulses to the hypothalamus, whence secretory fibers pass to the pars glandularis. Here it is proposed to review other data which also indicate that impulses from the central or peripheral nervous systems may control the secretion by the anterior pituitary of gonad-stimulating hormones into the blood stream.

Rosen and Shelesnyak (1937) produced pseudopregnancy in more than one-half of a group of rats as a result of the intranasal instillation of a solution of silver nitrate. This effect possibly is related to a reflex effect on the anterior pituitary. Other investigators have studied peripheral sympathetic nerves. Friedgood and Pincus (1935) stated that bilateral faradic stimulation of the cervical sympathetic nerves caused ovulation in 3 of 6 adult rabbits as well as clear-cut maturation of ova. In later work Friedgood and Cannon (1936) reported that bilateral cervical sympathetic stimulation by a

condenser-discharge method failed to cause ovulation but did bring about maturation of ova. They believed that the cervical sympathetics have only a limited control over the discharge of gonadotropic hormones by the anterior pituitary. Brooks (1937) was unable to prevent the ovulation following coitus in the rabbit by removing sense organs or parts of the central and peripheral nervous systems (such as the olfactory bulbs or the cerebral cortex or the sacral cord, the abdominal sympathetics, the uterus, and part of the vagina).

Diffuse powerful electrical stimulation applied to the brain or lumbosacral cord of the rabbit can cause ovulation, although the latter occurs 7–14 hours later than after coitus (Marshall and Verney, 1936). Harris (1936) applied a similar stimulus to the head of the adult female rat; as a result pseudopregnancy occurred in about 70 per cent of the animals. The same author (1937) was able to produce ovulation, sometimes associated with the formation of cystic or hemorrhagic follicles, by applying an electrical stimulus to the hypothalamus or pituitary of the rabbit. According to Haterius and Derbyshire (1937), who used a small bipolar electrode, a sharply localized area 5 mm. below the surface above and anterior to the optic chiasm causes ovulation when stimulated. There is an associated motor response (flexion of hind legs, pelvis, and trunk; elevation of tail). The authors used rabbits. Cahane and Cahane (1935–36) described histologic changes in the anterior pituitary and genital atrophy in 2 of 8 rats surviving a lesion made in the infundibulo-tuberal region of the hypothalamus.

Presumably impulses from the hypothalamus (or thalamus) pass down the stalk and provoke secretion of gonadotropic hormones when central stimulation is followed by ovulation and pseudopregnancy. However, the evidence is much less complete than that afforded by similar studies of the secretion of the diuresis-inhibiting hormone of the pars neuralis. Harris (1937) stated that lesions of the stalk were followed by genital atrophy in both male and female rabbits. According

to Westman and Jacobsohn (1937), this occurs in female rats as well as female rabbits; the effects, after section of the stalk, resemble those of hypophysectomy except that degeneration of the cells of the membrana granulosa does not appear. However, Brooks (1937–38), who used only female rabbits, concluded that the severing of the stalk, although preventing ovulation due to coitus and causing atrophy of the pars neuralis, had no other effect including possible actions on growth, maintenance of the genital tract, ovaries, thyroid, adrenal, etc. The ovaries contained ripe follicles from which ovulation occurred after the injection of pregnancy-urine. Brooks emphasizes that operations on the stalk may also seriously impair the vascular supply of the pituitary body. According to Keller and Hamilton (1937), breeding, pregnancy, parturition, and lactation can occur normally in the dog after the hypophysial stalk has been severed.

Vitamins and minerals in relation to the gonadotropic hormones of the anterior pituitary.—It is natural that the vitamin considered to be necessary for normal reproductive performance, vitamin E, should receive the most attention of those interested in the possible effects of vitamin deficiency on the pars glandularis. Extracts, such as wheat germ oil, containing a high concentration of vitamin E, possess no gonadotropic action (Verzár and others; Saphir, 1936). Marchesi (1935) stated that adult female rats on a diet deficient in vitamin E and otherwise sterile became pregnant and delivered the young normally after a suitable course of treatment either with anterior pituitary extract or prolan. The young died shortly after birth. Diakov and Křiženecký (1935), however, believed that the vitamin is necessary for the successful completion of pregnancy, although the administration of either prolan or anterior pituitary extract might bring about follicle growth and ovulation, and make possible fertilization and implantation in female rats receiving no vitamin E. The gonadotropic hormone(s) causing ovulation in oestrus rabbits is reduced in amount in the pituitary of the

adult female rat on a diet contraining no vitamin E (Row-
lands and Singer, 1936). The reduction is comparable to that
occurring on the sixteenth day of pregnancy in normal rats
(50–60 per cent of the normal value). The pituitary of ani-
mals which recover from the vitamin deficiency contains as
much as or more hormone than the normal female gland. Vi-
tamin-E deficiency is accompanied by no conspicuous change
in pituitary weight.[60]

According to Orent-Keiles, Robinson, and McCollum
(1937) a sodium-deficient diet brings about, in the female
rat, a delay in sexual maturity and a serious disturbance in
the oestrous rhythm as well as other phases of reproductive
physiology. The animals do not mate. Males, however, re-
main fertile for 2.5–3 months. To what extent pituitary func-
tion is altered is not known.

Riddle and Dotti (1936) concluded that pituitary gonado-
tropic hormone causes an increase in the concentration of
serum calcium in the pigeon (normal, hypophysectomized, or
thyroidectomized) but not after gonadectomy. Other pitui-
tary extracts, not containing gonadotropic hormone, were
without action. They believed that oestrogens but not andro-
gens had a similar action in the pigeon, fowl, and dog (but
not the rabbit); often their results were sufficiently irregular
as not to be convincing. Kozelka and Tatum (1937) found
that the injection of 150 rat-units (total dose?) of gonado-
tropic hormone lowered the serum calcium of rachitic dogs
1.7 mg. per cent (from 10.1 to 8.4 mg. per cent).

*Neoplastic growths and the gonadotropic hormones of the
pituitary body.*—Both Katz (1936) and Druckrey (1936–37)
concluded that pituitary gonadotropic hormones antagonize

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[60] Selye and Collip (1936) reported that rats on a "deficent diet" (50 per cent
ground beans, 50 per cent "Purina") went into permanent dioestrus with ovarian
atrophy. Inasmuch as the ovaries of such animals responded to prolan in a typical
fashion, the authors concluded that the diet led to a failure of secretion of gonado-
tropic hormone by the pituitary.

Teresa (1937) believed that the amount of gonadotropic hormone in the pitui-
tary of the mouse fed a diet lacking vitamin B is less than normal. This observation
is contrary to that of Marrian and Parkes in rats.

the growth of malignant neoplasms. Their reasons were the following: gonadectomy is followed by an inhibition of growth (including metastases) of such malignant tumors as tar cancer, the Jensen sarcoma, and the Flexner-Jobling carcinoma; this inhibitory effect is at its peak when the amount of gonadotropic hormone in the gonadectomized animal's pituitary is highest; the inhibitory effect of gonadectomy may be somewhat antagonized by an oestrogen; the injection of a gonadotropic extract (prolan, 5 rat-units on alternate days) also may inhibit tumor-growth in both normal and gonadectomized rodents. The report of Bischoff and Maxwell (1936) directly contradicts this interpretation as far as transplanted sarcomata (180 and R10) are concerned. Although injections of prolan or pituitary gonadotropic hormone produced marked changes in the gonads, they did not inhibit tumor-growth.

The metabolism of the gonadotropic hormones of the anterior pituitary.[61]—Freed (1935), supplementing previous reports, concluded that gonadotropic hormone, probably originating in the pars glandularis, is found in the urine of children more than 4–5 years old. The urine of children 10 years old contains as much hormone as the urine of adults. According to Frank and Salmon (1935), cyclic variations in the concentration of both follicle-stimulating hormone and luteinizing hormone can be detected in the blood and urine of normal women. They reported that the concentration of the hormones in the blood increased about the 9–12 day of the menstrual cycle and that a day or two later (10–14 day) there occurred

[61] Engel and Werber (1937), confirming Anderson and Haymaker (1935), found that tissue cultures of the pituitary of the mouse contain no detectable amount of gonadotropic hormone. The degree of growth of the typical epithelial cells is not affected by the previous treatment (e.g., gonadectomy) of the mouse furnishing the pituitary tissue (see also chap. i).

The relationship between the pituitary and the embryonic development of the gonads in the goat, ox, pig, and sheep was investigated by Daineko (1936).

Saxton and Loeb (1937), using the female guinea pig for assay, studied the gonadotropic effects of the pituitary of man in relation to sex, age, pregnancy, and lactation. Those interested should read the original report.

a rise in the urinary concentration of the hormones.[62] It must be emphasized that these reports may not be in accord with those of other investigators. The reports and discussions of Österreicher (1935) and Fluhmann (1937) should be read to correct any belief that various authors are in reasonable agreement as to the concentration of gonadotropic hormones in the blood or the excretion of the hormones in the urine of both children and adults. This is also true of the cyclic variations which may be found in the blood and urine of women.

The daily urinary excretion of gonadotropic hormone by normal men is probably greater than 6 rabbit-units (Friedman and Weinstein, 1937).

Anselmino and Hoffmann (1936) concluded that early in pregnancy small amounts of pituitary gonadotropic hormone are excreted in the urine. In the urine of patients with hyperemesis gravidarum an increased amount of pituitary gonadotropic hormone was believed to be excreted, whereas none of the hormone could be found in the urine of patients with eclampsia. These conclusions must be regarded only as suggestions, because detection of the pituitary hormones was based on the production of ovarian hypertrophy greater than 55–60 mg. in rats 30–35 days old (28–35 gm.). It was assumed that the prolan present produced a limited hypertrophy. A total number of only 54 rats was used and the possible synergistic effect of the secretion of the rats' pituitaries was disregarded. According to Tenney and Parker (1937), the urine of parturient women contains a pituitary-stimulating substance causing indirect gonadotropic effects. They believed that this substance could be distinguished from prolan which

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[62] The authors as well as Frank, Salmon, and Friedman (1935) performed their assays in normal rats. Their results should be confirmed (e.g., the presence of luteinizing hormone) in hypophysectomized rats (see also Guyénot and others, 1936). Evans and Simpson (1935) produced superovulation and even corpus luteum formation with extract of "menopause urine." To what extent these phenomena would have been observed in hypophysectomized rats is not known. Also, they agreed with others in their description of the synergistic effects of such extracts with prolan.

was completely precipitated by 5 volumes of alcohol, whereas under similar conditions only 20 per cent of the newly described substance could be recovered. Obviously, better data are needed to establish their conclusion.

Monnier (1936) found that lumbar or ventricular cerebrospinal fluid of patients with brain tumor (9 of 20) or other cerebral disease (3 of 10) stimulated the gonads of male or female immature mice. Such effects were never produced by normal cerebrospinal fluid. (Other reports are mentioned in the previous volume.)

Miscellaneous observations.—Emery (1937) reported that splenectomy in the rat does not alter various gonadotropic effects of "minimal strength" pituitary transplants. Gordon and others had reported differently but used prolan instead of a true anterior pituitary hormone.

THE PREPARATION, ASSAY, AND SPECIAL EFFECTS OF GONADOTROPIC PITUITARY EXTRACTS

The preparation and chemical nature of pituitary gonadotropic hormones.—The complex effects of pituitary gonadotropic extracts have led to equally complex interpretations of the number of hormones secreted. Even the generally accepted belief that separate follicle-stimulating and luteinizing hormones are secreted by the pars glandularis has not been proved with convincing thoroughness. Therefore, once a gonadotropic hormone has been isolated as a crystalline, chemically pure substance, it will be possible rapidly to decide many vexing questions of interpretation.

What data have been published recently still indicate that pituitary gonadotropic hormone(s) are proteins or substances of protein-like nature. Tryptic digestion (or heat to a far less extent) rapidly destroys pituitary hormones, causing ovulation in rabbits or testis-stimulation in immature doves (Riddle and others, 1936). On the other hand, tryptic digestion under proper conditions appears to bring about destruction of nearly all the luteinizing action of anterior pituitary extract

in the rat but permits the retention of the extract's follicle-stimulating effect (McShan and Meyer; Chen and van Dyke). Rowlands (1935) found that extracts of the beef anterior pituitary, tested by their ovulation-producing effect in rabbits, were not affected by "Merthiolate" (0.02 per cent) but deteriorated rapidly at room temperature (50 per cent loss in 9 days, 75 per cent loss in 23 days). Stored at $-2°$ C., such extracts lost less than 50 per cent of their activity after a year. Maxwell and Bischoff (1935), who doubt that there are two gonadotropic hormones, found that their pituitary extract was inactivated by 0.1 N NaOH (3 hours at 37° C.) but was only partially destroyed by treatment with 0.033 N NaOH or 0.1 N HCl under the same conditions. Mild oxidizing or reducing agents did not affect the hormone(s), whereas it was partially or completely inactivated by reagents reacting with amino, imino, or hydroxyl groups. Formalin treatment (4–10 per cent at pH 7–8) did not prevent luteinizing effects.[63]

The extraction procedure of Bates, Riddle, and Lahr (1935) utilized as an initial solvent 60 per cent aqueous alcohol at a pH of 9–9.5. Guyénot, Ponse, and Dottrens (1935) described methods—differential filtration, hydrolysis by acid, autolysis, peptic digestion—of separating follicle-stimulating ("auxogenic") hormone from luteinizing ("crinogenic") hormone. Evans and others, in two reports published in 1936, described methods for isolating from pituitary tissue specific extracts comprising (1) a substance stimulating the interstitial cells of the ovary or testis, (2) a luteinizing substance, (3) a follicle-stimulating substance which also stimulates the testicular germinal epithelium, and (4) a substance inhibiting or antagonizing the action of the follicle-stimulating substance (or of prolan or of the gonadotropic hormone of pregnant-mare serum). Revised methods, including necessary precautions, of extracting gondaotropic hormones from urine have recent-

[63] Hayward and Loeb (1937) studied the effects of pituitary tissue implanted after immersion for hours to days in strong solutions of sucrose, glycerine, or urea.

ly been published by Levin and Tyndale (1935), Thomsen and Pedersen-Bjergaard (1935–36), Palmer (1937), and Katzman (1937).

The assay of the gonadotropic hormones of the anterior pituitary.—The "unit" of a gonadotropic hormone, whether the assay be performed in the immature rat or in some other animal, is a term which remains without precision. Recently a start has been made by the National Institute for Medical Research (Great Britain) to set up provisional standards and to determine from the experience of widely separated investigators what methods of assay should be recommended. If standard preparations for assay and standard procedures of performing assays are agreed upon and adopted, units of gonadotropic activity designated by different authors can be evaluated with far more assurance than at present. Assay is affected by many factors, the importance of which varies with the source and nature of the gonadotropic agent. For example, the frequency of injection and the route of injection may greatly modify the response of the immature rat's ovary to pituitary gonadotropic hormone; however, Bates and Riddle (1936) found this not to be true of the effect of hormone on the pigeon's testis.[64] Other obvious factors are the size (or litter-size)[65] of the immature rat, diet, racial strain, ease with

[64] Bates, Riddle, and Lahr (1935) stated that the response of the immature dove's testis to gonadotropic extract is not affected by the presence or absence of luteinizing hormone.

[65] An example of work bearing on this factor is the report of Engle, Crafts, and Zeithamel (1937). The effect of the rat's rate of growth on the age and body-weight of vaginal canalization was investigated by comparing groups of individuals from litters of varied size—the rate of growth usually being inversely proportional to litter-size. The results were as follows:

LITTER-SIZE	OPENING OF VAGINAL ORIFICE (FIRST OESTRUS)	
	Age in Days	Weight in Grams
2–3	46.5	109.9
4–5	52.9	114.8
10–11	77.9	115.1
3–4 (yeast fed)	41.1	127.0

which the preparation used is metabolized, possible synergistic or antagonistic effects of substances in the extract, etc. There is increasing recognition of the inability to control the effects of the anterior pituitary secretion if normal animals are used for assay. Especially is it necessary to use hypophysectomized animals in testing extracts considered to have specific qualitative effects.

Investigations of the relationship between dosage of pituitary gonadotropic hormone and the response of the gonads
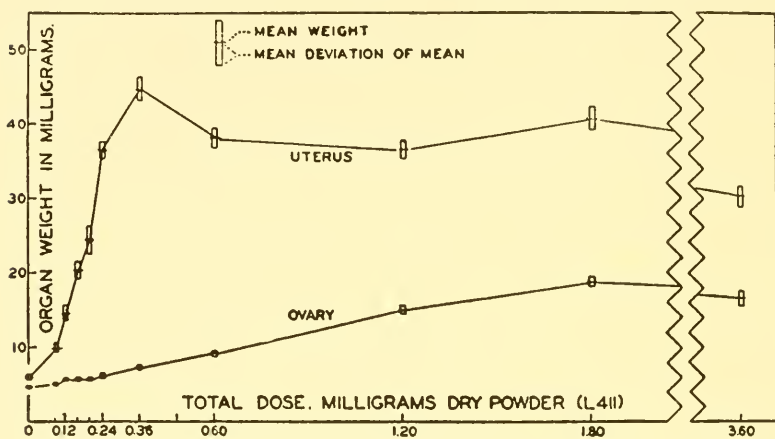
FIG. 14.—The effect of various doses of follicle-stimulating hormone of "castrate" urine on the weight of the ovary and uterus of the mouse. (From Levin and Tyndale, Endocrinology, **21,** 619–28 [1937].)

have been made recently by Deanesly (1935), Chow and Liu (1937), and Levin and Tyndale (1937). Deanesly recommended that the ovarian hypertrophy produced for quantitative assay of pituitary gonadotropic hormone should be represented by paired ovarian weights within a range of about 30–80 mg.[66] However, it has become increasingly clear that the use of ovarian weight as a basis for assay may have only a limited value. Levin and Tyndale found that the response of the uterus of the immature albino mouse to the follicle-

[66] After fixation in Bouin's fluid and partial dehydration (70 per cent alcohol).

stimulating hormone of "castrate" urine to be 5–10 times greater than that of the ovaries. They obtained data on the relationship between dose and uterine hypertrophy (see Figs. 14 and 15). In a later report Heller, Lauson, and Sevringhaus (1938) particularly studied the response of the immature rat's uterus. According to Bachman (1936), corpora lutea
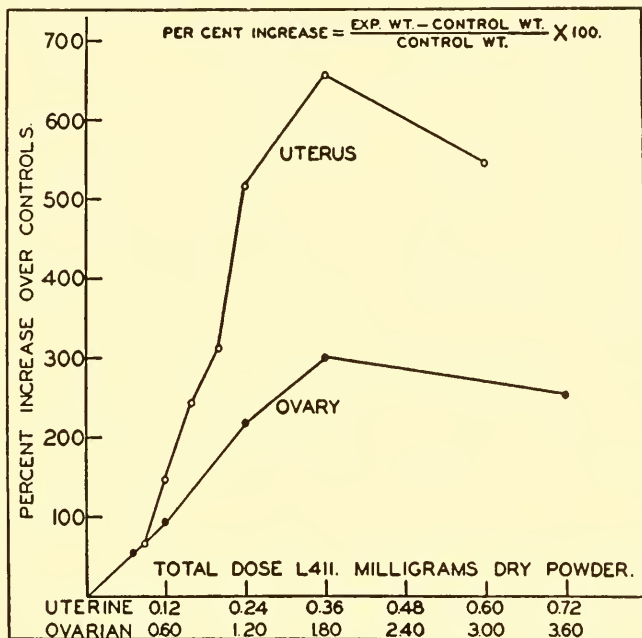
FIG. 15.—The change in weight of the ovary and uterus of the mouse, in terms of control weights, following various doses of follicle-stimulating hormone of "castrate" urine. (From Levin and Tyndale, Endocrinology, **21**, 619–28 [1937].)

without uterine changes may appear after the injection of gonadotropic extract (sheep pituitary extract, prolan) into very young rabbits. No effects are produced in rabbits less than 1.5–2 months old.

Special effects of gonadotropic pituitary extracts or related substances. 1. *The doctrine of antihormones.*—Since the publication of reports by Collip and his collaborators indicating

that the prolonged injection of gonadotropic extracts is followed by the production, at some unknown site, of "antihormone" which can be detected in the serum, numerous authors have made many further investigations of the phenomenon. The production of antihormone is of practical importance; for, if an injected extract produces antihormone, successful therapy may be thwarted and the patient's condition even may be worsened.[67] The other important question is the significance of possible antihormone balance to gonadotropic and other hormones secreted by the gland *in situ*. Chiefly from experiments in parabiotic animals there is good evidence against the view that the body may produce its own antihormone to inhibit excessive secretion by a gland like the anterior pituitary. Also the evidence from artificially introduced hormone is by no means concordantly in favor of the antihormone hypothesis.

Usually the prolonged injection of a gonadotropic extract is followed by progressively less effect, until finally the ovaries or testes of the injected animals may actually be smaller than those of animals not receiving treatment. Antihormone can then be readily detected in the serum by its inhibitory effect on the gonadotropic action of the extract when the serum and extract are injected into fresh animals. An attempt again to stimulate the gonads of the animals receiving the prolonged injections after a period of rest either fails or produces only a slight change. Most investigators are in agreement with these general statements. However, the interpretation of the phenomenon is a matter of disagreement which perhaps cannot be settled from a consideration of the published data.

One obvious basis for the development of antihormone in response to the long-continued injection of gonadotropic ex-

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[67] Spence, Scowen, and Rowlands (1938) concluded that the injection into human beings of prolan (1,000 rat-units weekly) or extract of the pig pituitary (30–50 R.U. weekly) for varying periods up to 7 months was followed by the appearance of no "serious amount of anti-gonadotropic activity" in the serum.

Rowlands and Parkes (1937) suggested that antihormone obtained from serum of suitably injected animals might be used to lessen the effects of hormones secreted by the hyperactive pituitary.

tract is the production of immune bodies by specific or non-specific protein included in impure extract. Max, Schmecke-bier, and Loeb (1935), for example, believed that extraneous protein was responsible for the refractory state of their guinea pigs to extract injected after 4–6 weeks of treatment. Others have attempted, without success, to correlate the presence or development of typical immune bodies with the development of antihormone. Usually the development of antibodies does not parallel the development of antihormone (Collip, 1935; Gustus, Meyer, and Dingle, 1935; Brandt and Goldhammer, 1936). Sulman (1937) who used prolan or pregnant-mare serum as possible antigens concluded that these substances, injected into rabbits, behaved neither as antigens (reaction with antisera, including complement-fixation) nor as hap-tenes.[68]

A great deal of work is represented by investigations of the species (and source) specificity of antihormones due to the injection of gonadotropic extracts.[69] If gonadotropic extracts were highly species specific, this fact would constitute evidence that they are artificially produced by some mechanism analogous to antigen-antibody reactions. The results are most varied and indicate that, in the hands of different investigators—and sometimes in the hands of the same investigator—gonadotropic extracts may or may not be species specific.[70] Chen (1937) found that the ordinary proteins of sheep or human serum, injected as serum repeatedly into

[68] B. F. Chow informs me that failure to secure a complement-fixation reaction does not necessarily indicate that a substance is not antigenic and that the antigenic effects of a highly potent antigen (e.g., prolan) may not be recognized unless relatively large doses are injected.

[69] Gonadotropic extracts, both for producing antihormone and for detecting the presence of antihormone, have been obtained from the following sources: pituitary tissue of man, the horse, ox, pig, or sheep; blood, placenta, or urine of human pregnancy; serum or urine of equine pregnancy; urine of women past the menopause.

[70] Parkes and Rowlands (1937) concluded there is at least class specificity toward antihormones. They were unable to prevent the thyrotropic or gonadotropic effects of mammalian extracts in fowls by first injecting rabbit serum rich in antihormone as judged by tests in mammals.

rabbits, do not cause the production of substances behaving like antihormone toward gonadotropic extracts of sheep or human pituitary. Several recent authors concluded that various gonadotropic extracts from the pituitary, blood, or urine of different animals could produce antihormone which is not species specific (Gregerson, Clark, and Kurzrok; Parkes and Rowlands, 1936; Collip, Rowlands, Thompson and Cushing, 1937). These experiments are the most complete and extensive. However, mixed results may be obtained, so that some extracts produce antihormone which appears to be partially or completely species characteristic (Collip, Rowlands, 1937). Finally, several observers found, at least with their preparations, that antihormones toward gonadotropic extracts inhibit the effect only of extracts of tissue or urine of the animal of the same species (Fluhmann, 1935; Gustus, Meyer, and Dingle, 1935; Brandt and Goldhammer, 1936). As far as pituitary gonadotropic extracts are concerned, the weight of evidence appears to be against the view that antihormone is species specific. Perhaps there is true "species specificity" when extract of human pregnancy-urine (prolan) or pregnant-mare serum is used as an "antigen" (Rowlands). "Source specificity" is believed by Rowlands (1938) to be complete in the case of pregnant-mare serum, although others (e.g., Thompson and Cushing) have obtained different results. It is probable that, if antihormone formation is analogous in some phase or phases to the formation of immune bodies, the problem is rendered more complex and more difficult to interpret than most immune reactions, because of the possibility that the hormone "antigens" are more complex than is usually suspected (see Rowlands, 1938).[71] The con-

[71] The method of detecting antihormone (cf. failure of ovarian hypertrophy in the rat and failure of ovulation in rabbit) may determine whether the result is positive or negative. Using an extract of the anterior pituitary of the ox as "antigen," Rowlands (1937–38) found that its antihormone antagonized the gonadotropic action of sheep pituitary extract (ovarian hypertrophy in rats), whereas Parkes and Rowlands (1936) found this not to be the case when they used the production

sidered opinion of investigators like Rowlands is that an immune-like reaction has been neither proved nor ruled out.

Several attempts to inhibit the effects of gonadotropic hormones secreted by the pars glandularis *in situ* have been successful and constitute evidence favorable to the view that antihormone-formation is important physiologically. Parkes and Rowlands (1936) showed that the ovulation which usually follows coitus in the rabbit can be prevented by the intravenous injection, 15 minutes after mating, of rabbit serum containing a high titer of antihormones toward the gonadotropic principles in ox anterior pituitary extract. An extension of this study by Rowlands (1937) indicated that such serum containing antihormone, although not interfering with corpus luteum formation, pregnancy, or lactation in the mouse or rat, did have the following antigonadotropic effects: (1) it prevented ovulation in the prepubertal rat, (2) it produced atrophy of the reproductive organs of the adult male rat, and (3) it could prevent, in the rabbit, ovulation or corpus luteum formation or, in pregnant animals, implantation of the blastocyst or fetal survival. According to Collip (1937), antihormone-containing serum prevents oestrous cycles in rats. Also he believed (1935) that antihormone-like substances may appear in the blood spontaneously. Thompson and Cushing (1937) caused marked ovarian atrophy in growing rats by injecting serum containing antihormone (sheep pituitary extract as "antigen" for about two months). Hisaw, Hertz, and Fevold (1936) concluded that, although the continued injection of sheep pituitary extract might be accompanied by a refractory condition of the ovaries in juvenile monkeys (*Macaca mulatta*), only temporary effects were produced in adults. They believed that the antihormone pro-

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of ovulation in the rabbit as an indication of gonadotropic effect. However, Parkes and Rowlands used a saline suspension of the sheep pituitary body.

More clear cut are the experiments of Rowlands (1938) who found that the serum of an animal receiving a course of injections of pituitary extract might augment the effects of the extract in immature rats (ovarian hypertrophy) and yet inhibit the action of the extract in rabbits (ovulation response).

duced in response to sheep pituitary extract does not inhibit the action of gonadotropic hormone secreted *in situ* by the monkey's pars glandularis.

The strongest evidence against antihormone-production as a physiological mechanism is afforded by experiments with animals living parabiotically, as has been emphasized re-

CASTRATE   HYPOPHYSECTOMIZED

FEMALE   FEMALE

Body Weight 250 G
Thyroid   23 MG
Adrenals   64 MG
Access   390 MG
Ovaries   -   -

Body Weight 180 G
Thyroid   13 MG
Adrenals   16 MG
Access   1350 MG
Ovaries   416 MG
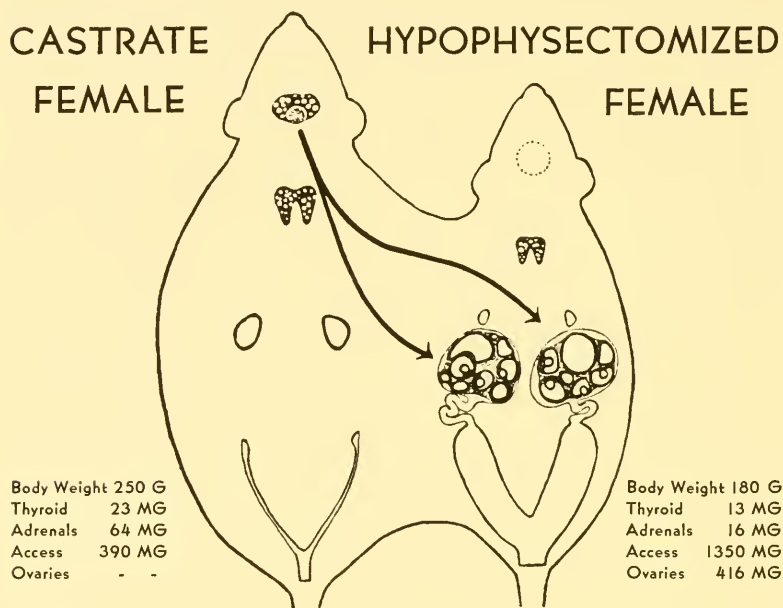
Fig. 16.—Diagram illustrating the ovarian changes which occur as a result of parabiosis between a hypophysectomized rat with intact ovaries and a spayed rat which otherwise is normal. No antihormone antagonizing gonadotropic hormone is produced. (From DuShane, Levine, Pfeiffer, and Witschi, Proc. Soc. Exp. Biol. Med., **33,** 339–45 [1935].)

peatedly both by the author and by other investigators (e.g., Doisy, Martins, Witschi). Du Shane and others (1935) therefore consider antihormone formation a type of immune-body reaction. Parabiosis between a spayed or castrated rat and a normal or hypophysectomied female (e.g., ♀ ♀, ♂ ♀, ♀ ♀ h) is accompanied by a marked follicle-stimulating effect of the gonadotropic hormone secreted principally by the

gonadectomized partner's anterior pituitary. Large cystic ovaries are developed—a phenomenon which apparently proceeds indefinitely (e.g., 15 months). In response to this endogenous gonadotropic hormone formed in great excess there is no compensatory production of antihormone (see Fig. 16). Finally, it must be realized that potent gonadotropic preparations, although administered for a prolonged period, do not necessarily bring about refractoriness of the "end-organ" (e.g., the ovary) with atrophy as is so commonly the case. Katzman, Wade, and Doisy (1937) inserted homo-implants of the pituitary into female rats for 210–75 days. At the end of the period of treatment the ovaries still were enlarged, and there was no gonadotropic (or thyrotropic) antihormone in the blood.[72] Fluhmann (1936) observed that a gonadotropic extract of the blood of pregnant women still maintained a marked ovarian hypertrophy in rats receiving injections for as long as a year.[73] In Thompson's experiments (1937) sheep received, for six months, injections of a sheep pituitary extract which readily produced gonadotropic antihormone in other species of animals. Yet none could be clearly detected in the blood of the sheep.

2. *The inhibition of gonadotropic effects by substances other than antihormones.*[74]—Extracts of the pituitary body may, under suitable conditions, antagonize the action of gonadotropic substances such as prolan, pregnant-mare serum, and gonadotropic pituitary extract. To this hypothetical substance Evans has given the name "pituitary antagonist." Its inhibition of gonadotropic effect is most characteristically manifested when administration is intraperitoneal. Evans and others (1936) have described methods of preparing the substance free from follicle-stimulating or luteinizing effects.

[72] There was no significant alteration in the weight of the adrenals, thyroid, or pituitary (see also the similar experiments of Artemov, 1937).

[73] The ovaries contained large corpora lutea, lutein cysts, and developing follicles. There was hypertrophy of the pituitary with associated histologic changes.

[74] See also the effects of lactogenic extracts (pp. 98–99).

The authors concluded that it antagonizes the action of folli-cle-stimulating hormone but not luteinizing hormone and that it acts independently of the pituitary, thyroid, or adrenals. Some of its described effects suggest that it is luteinizing hormone: it has no action on the ovaries of normal immature rats, but it causes or permits extensive luteinization of the ovaries of adult rats and prolongs pregnancy, if injected in the last half of pregnancy. Evans and his colleagues suggest that such a substance may be important physiologically. It is obvious that its presence in extracts may complicate all studies of the effects of gonadotropic extracts, including investigations of antihormones (see the following section).[75] Leonard, Hisaw, and Fevold (1935) concluded that the inhibitory substance is associated with luteinizing hormone, although follicle-stimulating hormone, also injected intraperitoneally, might produce some inhibition. It is the belief of Jensen (personal communication) that luteinizing hormone, "pituitary antagonist," and "interstitial cell stimulating hormone" are one and the same principle.

Freud (1937) believed that he had detected an "antiluteogenic factor" in extract of the pars glandularis of the ox. He suggested that the absence of this substance accounts for the persistence of corpora lutea in hypophysectomized rats. (Bunde and Greep [1936] considered this to be owing to a lack of luteinizing hormone or some substance associated with it.) Two early pregnancies in rats were interrupted by intraperitoneal injections of the extract—a fact which the author interprets as supporting his view that the injected substance antagonized the luteinizing hormone.

3. *The augmentation of the effects of gonadotropic extract.*—A variety of substances may potentiate or augment the action of a gonadotropic extract. For example, the hypertrophy

[75] Evans concluded that the immature pigeon's testis is very sensitive toward gonadotropic extract, because it is unaffected by "pituitary antagonist" (see also Bates, Riddle, and Lahr, 1935).

of the immature rat's ovary, caused by a follicle-stimulating extract, is greatly increased if a luteinizing substance also be given. A puzzling recent observation of great interest is the potentiating action, at certain times, of the serum of animals receiving a prolonged course of injections of gonadotropic pituitary extract to produce antihormone which, of course, has the opposite action. This phenomenon has been studied by Collip (1937), Thompson (1937), and Rowlands (1938). Thompson's experiments illustrate how this information was obtained. A horse and two dogs received repeated injections of sheep pituitary gonadotropic extract. The effects of their sera on the gonadotropic action of the extract in hypophysectomized or normal immature rats was ascertained at intervals of 7–20 days. Finally, the sera were found to contain a substance or substances which augmented the action of the extract on the immature rat's ovary about threefold. Sera which were obtained 50–80 days after the injections were started had the maximum augmenting effect. The active substance(s) was in the pseudoglobulin fraction which also contains immune bodies and antihormones, if these are present. Thompson suggested that an antihormone to "pituitary antagonist" (see the foregoing section) may have been formed. Rowlands is inclined to concur with this view and enumerates reasons in support (specificity of effect for pituitary gonadotropic extract only, especially of extracts probably rich in "antagonist," lack of phenomenon with nongonadotropic pituitary extracts with other effects, etc.).[76]

By direct extraction of the anterior pituitary, a substance augmenting the action of certain gonadotropic extracts (e.g., follicle-stimulating extract as extract of urine of women after spaying or after the menopause, endometrium of the preg-

[76] In Collip's experiments (sheep pituitary extract as "antigen" injected into lambs) antihormone was demonstrated later. Katzman, Wade, and Doisy (1937) who unsuccessfully attempted to produce antihormone effects by pituitary homoimplants in rats, remarked that the serum obtained at the end of treatment (7–9 months) augmented the gonadotropic effects of implants.

nant mare, etc.) can be secured .This was named "pituitary synergist" by Evans and others. There is not satisfactory evidence that this substance is different from what others call "luteinizing hormone." Recent work has been reported by Evans and Simpson (1935), Saunders and Cole (1935), and Lein (1937).

A number of substances, if injected with pituitary extract, is capable of augmenting the action of pituitary gonado-tropic hormone. In addition to tannic acid (recent studies by Bischoff, 1937; and Fevold, Hisaw, and Greep, 1937) and $ZnSO_4$ (recent studies by Saunders and Cole, 1935; Fevold, Hisaw, and Greep, 1936; and Emery, 1937), which were previously known to have this action, approximately a dozen new substances have been shown also to be effective. These include $(CH_3COO)_2Cu$ and $CuSO_4$ (Fevold, Hisaw, and Greep, 1936–37; Emery, 1937; and Pfeiffer, 1937), "Merthiolate" $(C_2H_5HgSC_6H_4COONa)$, a germicide (Chen and van Dyke, 1938), yeast extract and yeast ash (Fevold and others, 1936), blood, hemoglobin, or heme (Casida, 1936; McShan and Meyer, 1937), casein and egg-albumin (Saunders and Cole, 1935), and a miscellaneous group of substances only crudely characterized (Hellbaum, 1936).

Figure 17 illustrates how strikingly the gonadotropic effect of an extract may be augmented by a foreign chemical mixed with the extract before injection. Until there is better evidence to the contrary, it is probable that this group of potentiating substances acts by interfering with the absorption of hormone, thus decelerating excretion (and possibly destruction) and prolonging the action of each dose.[77]

[77] Fevold, Hisaw, and Greep (1936) were inclined to believe that CH_3COOCu catalyzes the synergistic effects of follicle-stimulating and luteinizing hormones. In their earlier work, they reported that the intravenous injection of yeast extract (10–15 "grams-equivalent") or $(CH_3COO)_2Cu$ (10 mg.) can cause ovulation in the rabbit. Pfeiffer (1937) concluded that the injection of a solution of $CuSO_4$ has no effect on gonadotropic hormone secreted by the rat's pituitary *in situ*.
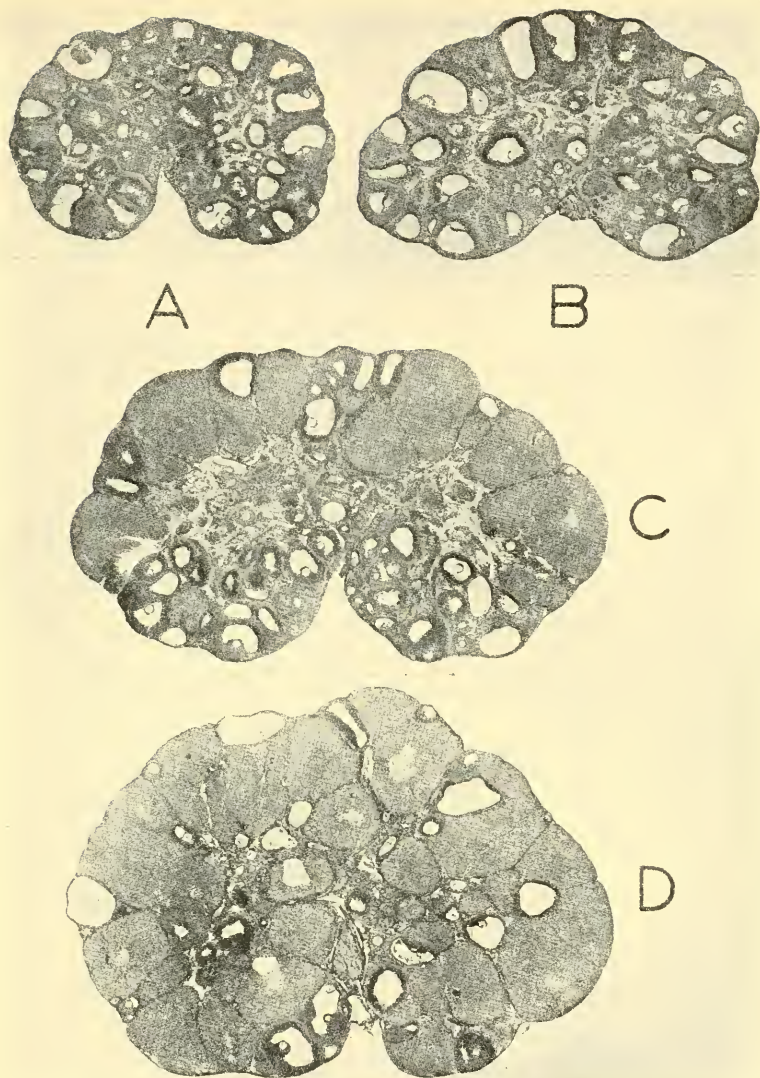
Fig. 17.—The potentiation of the response of ovaries of littermate rats as a result of the addition of "Merthiolate" to the pituitary gonadotropic extract injected. The rats were 26 days old at death and weighed 68 gm., except D, which weighed 54 gm. (From Chen and van Dyke, J. Pharmacol. exp. Therap., **62,** 333–45 [1938].)

Rat	Total Dose of Pituitary Gonadotropic Extract (Mg.)	Percentage Merthiolate in Solution of Extract	Weight of Both Ovaries (Mg.)
A..............	0	0	17.27
B..............	2.0	0	25.71
C..............	2.0	0.02	46.90
D..............	2.0	0.075	83.59

THE PITUITARY BODY

SUMMARY

Anterior pituitary secretion is a necessary condition of normal function of the gonads of all classes of vertebrates. How this necessary condition is implemented in the living animal has been of prime interest to a host of biological investigators, both seasoned and newly recruited. Although experiments have been performed in all classes of vertebrates—fishes, amphibia, reptiles, birds, and mammals—there still remain lamentably great gaps in our knowledge of the physiology of gonadotropic hormones. It is an unenviable task to summarize the work, because unifying working concepts either are lacking or may be widely used without equally wide recognition of their inadequate experimental foundations.

Discussion is difficult if there is not agreement on the probable number of gonadotropic hormones. Yet no investigator has succeeded in preparing a gonadotropic hormone in pure form. Partial purification has apparently been achieved and there continues to be evidence that there are two gonadotropic hormones: one facilitating follicle-growth and maturation (follicle-stimulating hormone), the other promoting the conversion of the cells of the membrana granulosa and thecae into lutein cells (luteinizing hormone). Both hormones are said to be necessary to produce ovulation. There is evidence that what is called follicle-stimulating hormone maintains spermatogenesis in the testis, whereas luteinizing hormone nurtures the interstitial cells of Leydig, whence arises "male hormone."[78] Some authors would lengthen the list further

[78] However, other data suggest different interpretations. Observations which must be reconciled are as follows: (1) follicle-stimulating hormone maintains the germinal epithelium, whereas the interstitial cells require luteinizing hormone for normal function (immature hypophysectomized male rats); (2) either hormone will support spermatogenesis, but only luteinizing hormone maintains the interstitial cells (mature hypophysectomized male rats); (3) spermatogenesis can take place normally in the absence of the pituitary, provided that a suitable androgen ("male hormone") is injected early enough after operation (mature hypophysectomized male rats); and (4) the pituitary of the normal male rat secretes only follicle-stimulating hormone (at least the secretion of luteinizing hormone has not been detected in the living animal, although small amounts of luteinizing hormone may be recognized by implanting the male pituitary).

with newly named (but not necessarily newly described) hormones, so that its total would be five or more instead of two. To recall only the example of the number of "corpus luteum hormones" once thought to exist before the pure substance had been isolated is to recognize the continued need for caution in discussing the number of gonadotropic hormones secreted by the pars glandularis. At present, there is probably nothing that will further rational interpretation and real advancement in this field as much as the isolation of a gonadotropic hormone of the anterior pituitary in a satisfactorily pure state.

Much of the recent data requires no reconsideration here. Descriptions of the effects of destruction or removal of the pituitary body supplement former reports as to the atrophic changes which dramatically follow in the ovaries, testes, and secondary sexual organs. Other experiments have increased our knowledge of the effects of pituitary tissue or extracts on the sexual organs of many different animals. It is known more accurately that even a short period of pituitary deficiency may markedly lessen the sensitivity of the gonads toward gonadotropic hormone. Also it is of interest that the persistence of corpora lutea in hypophysectomized rats appears to be due to the lack of an anterior pituitary hormone.

Physiological evidence of the nervous control of the secretion of gonadotropic hormones has been greatly strengthened in the past few years. In birds, and at least in some mammals, photic stimuli may elicit the secretion of gonadotropic hormones, which in turn stir the gonads into activity. Probably "light" reflexly stimulates the secretory nerves of the pars glandularis by impulses arising in the optic nerves, whence they are guided down fibers of the stalk by one or more groups of neurons in the diencephalon. In animals without precise seasonal variations in sexual, and hence pituitary, activity photic stimuli do not play such an evident role. However, diffuse or sometimes sharply localized stimulation of the brain may be followed by the release of gonado-

tropic hormone from the anterior pituitary as shown by ovulation in an animal like the rabbit. Other peripheral nerves like those of the sympathetic system may be part of an afferent arc, but their significance is not clear.

Great interest has been shown in the hormonal control of the secretion of gonadotropic hormones, especially as far as the internal secretions of the ovaries and testes may here be important. There is much data to suggest that surges or recessions of secretion by the anterior pituitary causing the growth or decay of gonadal activity (e.g., oestrous cycles) may be related to the absence or presence of internal secretion(s) of the gonads such as oestrogen from the ovaries. The regulation of the secretion of gonadotropic hormones by the pars glandularis may well depend upon a delicate, complex mechanism, partly hormonal and partly nervous. Also it is probable that the relative importance of the nervous system and of hormones of the gonads varies in different animals. The reader can easily diagrammatize a self-regulating physiological unit consisting of the pars glandularis, the gonads, and the nervous system. However, he cannot safely picture this unit in any detail. The known hormones characteristic of the gonads vary enormously in their apparent "regulating" (usually depressing) effect on the formation of gonadotropic hormone by the anterior pituitary. Oestrogens far excel androgens in potency; progesterone (from the corpus luteum) appears to be of slight importance.

The relation of adrenal cortical secretion to the phase of pituitary physiology under discussion is obscure because so many variables affect experimentation. Thyroid secretion perhaps is not of great significance; its usual effect, if any, is to lessen the action of follicle-stimulating hormone. How much regulation of the liberation of gonadotropic hormones by the pars glandularis is effected by the gland's own lactogenic hormone can be judged better when experiments have been performed with the recently isolated lactogenic principle.

Much has been written and continues to be written concerning "antihormones." There can be no question that gonadotropic extracts, if repeatedly administered in their present state of impurity, may cause at an unknown site the production of substances circulating in the blood and antagonizing the effects of pituitary extracts. However, other experiments furnish arguments, so far not refuted, that such substances are not formed in response to gonadotropic hormone secreted by the intact gland.

CHAPTER IV

THE GONADOTROPIC HORMONES ASSOCI-
ATED WITH PREGNANCY OR
CERTAIN NEOPLASMS[1]

GONADOTROPIC hormones associated with preg-
nancy or with neoplasms are not secreted by the
pars glandularis of the pituitary body. In pregnant
women, as well as in other pregnant mammals in which their
presence has been demonstrated, the characteristic hormone
probably originates in the epithelial cells of the chorion.
Neoplasms, such as certain tumors of the testis, also may
secrete gonadotropic hormones; neoplasms originating in the
chorion almost invariably liberate large amounts of such sub-
stances into the blood stream. The effects of all these sub-
stances differ in one or more ways from those of gonado-
tropic hormones secreted by or extracted from the pars
glandularis.

Most of the published reports deal with the gonadotropic
hormones of the pregnant woman and the pregnant mare.
Presumably, the important function of such hormones in
pregnancy is to insure the maintenance of an ovarian func-
tion favorable to the pregnancy. Inasmuch as the secretion
of the corpus luteum has been shown—especially in the earlier
part of pregnancy—to be vital for the continuance of preg-
nancy in many mammals, the luteinizing effects of the
chorionic hormones have been especially emphasized. In what
mammals, other than man and the horse, is there new evi-
dence for the secretion of chorionic hormone in pregnancy?
Heretofore there has been doubt as to the presence of gonado-
tropic hormone in the urine of the pregnant monkey. How-

[1] See also chaps. i and iii or refer to the Index.

[124]

ever, Hamlett (1937) has shown that the urine of the pregnant macaque about the 19–25 day of pregnancy may contain detectable amounts of gonadotropic hormone. It is probable that gonadotropic principles secreted by the chorion will be demonstrated in other pregnant mammals by future investigation.[2]

No gonadotropic hormone could be found in the serum of the pregnant ewe (Cole and Miller, 1935) or in the milk of the pregnant cow (total dose of 1.2 cc. in immature mice initially 17 days old; Weisman, Kleiner, and Allen, 1935). These reports supplement those reviewed in 1936.

THE GONADOTROPIC HORMONE (PROLAN) ASSOCIATED
WITH PREGNANCY IN WOMEN

New observations on the metabolism of prolan.[3]—All the recent observations support the view that prolan is secreted by the chorionic cells (Bourg and Legrand, 1935; Philipp and Huber, 1936; Kido, 1937). Most of the experiments were performed with implants. Kido observed the action of human placenta which survived transplantation in the anterior chamber of the female rabbit's eye. The secreted hormone affected the animal's ovary and could be detected in the urine.

The most striking new fact clearly demonstrated in respect of the urinary excretion of prolan is that an enormous excretion is observed about the 50–60 day following the last menstrual period (Browne and Venning, 1936; Evans, Kohls, and Wonder, 1937). Figure 18 is reproduced from the article of Browne and Venning. The highest figures reported by these authors are 100,000–300,000 rat-units per liter of urine in comparison with a later fall to about 3,000 rat-units per

[2] E.g., see Astwood and Greep (1938).

[3] See chap. v and Table VI of the earlier volume. Guercio (1936) believed that prolan can be detected in the saliva of pregnant women; however, this was denied by Weisman and Yerbury (1936).

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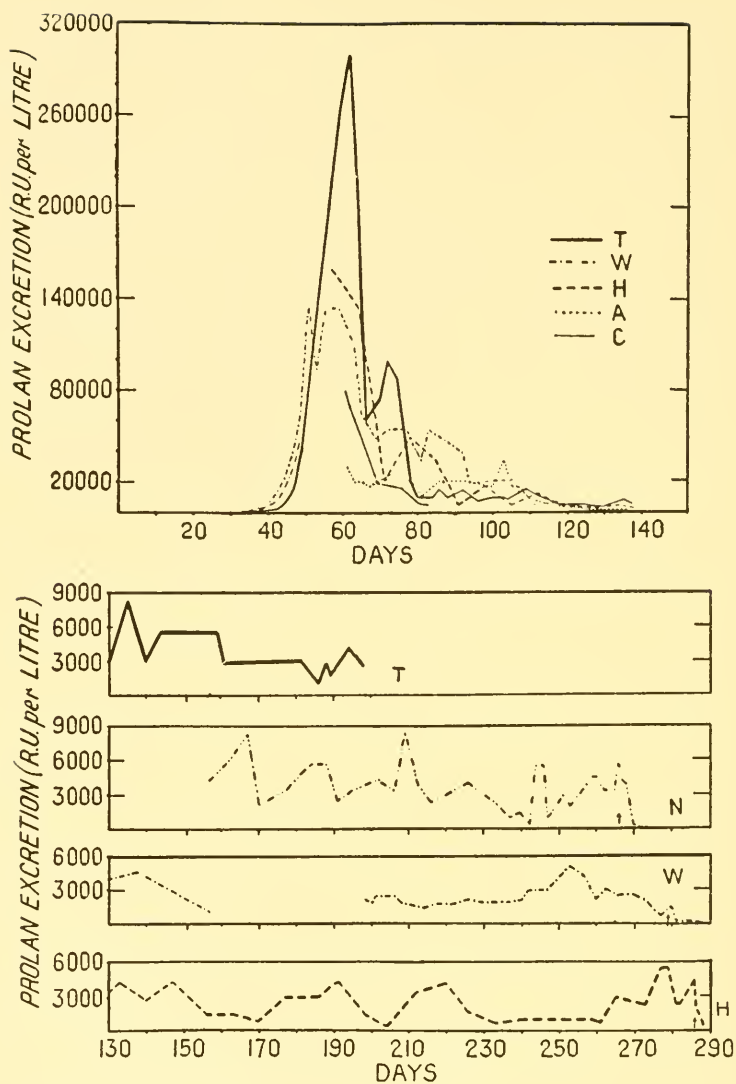
Fig. 18.—The excretion of gonadotropic substance(s) in the urine during pregnancy. Days are counted from the first day of the last menstrual period. The termination of pregnancy is indicated by arrows. (From Browne and Venning, Lancet, 231, 1507–11 [1936].)

liter, a concentration which persists after 120 days.[4] The rapid rise is prevented by fetal death or if the fetus is dying. Less accurate studies have been reported by Bourg and Legrand (1935), Ehrhardt (1936), and Spoto (1936). Bourg and Legrand also investigated the concentration of prolan in the serum and placenta. Their results justify the belief that the peak of urinary excretion coincides with high concentrations of prolan in the serum and placenta. (Ehrhardt likewise concluded that the concentration of prolan in the urine and serum is about the same.) The concentration of prolan in the amniotic fluid was found to be 7–33 per cent of that in serum.[5]

Smith and Smith (1935) have again pointed out that high concentrations of prolan in the serum are associated with toxemias of pregnancy, including eclampsia. However, Bourg and Legrand (1935) as well as Ehrhardt concluded that, although this is true of what are termed toxemias, an abnormally high prolan titer may not be found in the serum in eclampsia.

Some aspects of the fate of prolan after its administration to normal men or animals have been investigated. Friedman and Weinstein (1937) found that no more than 20 per cent of a dose of prolan injected intramuscularly into men could be recovered in the urine. After large doses by mouth (8,000–42,500 rat-units), none was detected in the urine. Stamler (1937) made other observations in the dog and the gelding. New experiments in rabbits were reported by Lip-

[4] Evans, Kohls, and Wonder observed maximum excretions of 75,000–1,040,000 rat-units in 24 hours compared with 2,600–15,000 rat-units at other times.

[5] The convenient and accurate methods of diagnosing pregnancy are those depending upon ovarian changes in immature rodents or ovulation in adult isolated rabbits. Intracutaneous tests in the patients themselves are of no value (Schneider and Cohen, 1937). Although chromatosome-dispersing ("melanophore-expanding") hormone is found more frequently in the urine of pregnant women, its presence is not reliable as indication of pregnancy (Mandelstamm, 1935; Jores, 1936; Bruckmann, 1937; Raza and Spurrell, 1937). Dychno (1936) considered such a test reliable.

For descriptions of a method based upon a color-reaction in urine see Visscher and Bowman (1934) and Friedrich (1936).

schütz, Fuente-Alba, and Vivaldi (1935). Tissue fixation or destruction of the hormone was indicated by the fact that 10 hours after intravenous injection, 30 per cent of the prolan had disappeared from the blood of nephrectomized rabbits; 80 per cent was lost in normal rabbits. Nizza and Berutti (1936) compared the changes in one intact ovary with the other which was transplanted into a second rabbit 30–120 minutes after the injection of urine of pregnancy. The differences appeared to be quantitative.

The gonadotropic effects of prolan in fishes, amphibia, and reptiles.—Some of the effects of prolan in cold-blooded animals have been described already.[6] Schreiber (1935) reported that the administration of prolan to immature eels can cause changes characteristic of testicular maturation, including the differentiation of spermatogonia into normal spermatozoa. According to Morosowa (1936), perch (November to March; weight 250–750 gm.) receiving prolan, although kept in water at 6–9° C., produce ripe eggs and spermatozoa, from which fertilized eggs can be secured. Shapiro (1936) demonstrated that in the toad, *Xenopus laevis*, the injection of prolan evoked amplexus in animals which otherwise were in a state of complete sexual inactivity. Ovulation, oviposition, and fertilization occurred. The offspring were raised to the tadpole stage. Turner's experiments (1935) were performed with the lizard, *Eumeces laticeps*. During the season of involution of the gonads, the injection of prolan (20 rat-units twice daily for 20 days) caused hypertrophy of the testes and the epididymides with the production of mature spermatozoa. Such treatment caused enlargment of the oviducts but had no effect on the ovaries. When the animals were active sexually, the response was much smaller.

The effects of prolan in warm-blooded animals.[7] 1. *Male*

[6] See chap. iii and the Index.

[7] Prolan is without demonstrated action on the gonads of birds (see pp. 52, 58). Schunterman (1935) declared that an intravenous injection of an extract of digitalis evoked emesis less frequently in pigeons which had received 2 units of prolan intramuscularly 10 minutes before.

mammals.—In normal male mammals, the typical effects of prolan—best observed in immature specimens—are on the interstitial cells of the testis (cells of Leydig). These secrete "male hormone," which is probably testosterone, at a more rapid rate so that the secondary sexual organs, such as the epididymides, seminal vesicles, and prostate, undergo abnormal hypertrophy and, histologically, may resemble the organs of adult animals. Such changes, of course, are absent, if the prolan-sensitive cells have been removed by castration. In immature mammals prolan does not initiate spermatogenesis. In adult animals, however, prolan, if administered immediately after operation, will maintain spermatogenesis after hypophysectomy (Smith and Leonard). This probably is due to the fact that the secretion of androgenic hormone by the interstitial cells continues as a result of the injection of prolan. It is well known that androgens by themselves may have this effect (see chap. iii). This fact probably accounts for the spermatogenesis which may be initiated in the ground squirrel (*Citellus tridecemlineatus*) by the injection of prolan at times of seasonal involution of the gonads (Baker and Johnson, 1936; Wells and Moore, 1936).

Other reports not reviewed previously are those of van Os (1936) and Kuschinsky and Tang (1936). Van Os could not bring about spermatogenesis in the testes of rats in which testicular degeneration had followed vitamin-A deficiency or cryptorchidism. Kuschinsky and Tang stated that the typical effects of prolan (seminal-vesticle hypertrophy, no consistent effect on testicular weight) could be observed in rats receiving prolan when only 6–13 days old.

2. *Female mammals.*—In female mammals the most striking effect of prolan is on the cells of the corpus luteum or on the cells of the theca interna—parent cells of corpora lutea. It may appear that follicle growth is stimulated, and some authors believe that prolan is composed of an "A" component, stimulating the follicle, and a "B" component, causing luteinization. Good evidence that both components

exist has never been offered. It is more simple and more accurate to consider that prolan is primarily a luteinizing gonadotropic hormone. Its presumed follicle-stimulating effects are seen in animals with intact hypophyses which contribute the important, and perhaps the only, share in bringing about follicle-stimulating effects. Anterior pituitary secretion is of great importance in permitting the recognition of the luteinizing effects of prolan. In hypophysectomized female rats, prolan may cause hypertrophy of the cells of the thecae and interstitium, with which may be associated a persistent oestrus; it does not bring about follicular growth.

Kuschinsky and Tang (1935) described luteinization of the ovaries of rats receiving large doses (25 rat-units daily) during the second week of life. A deciduoma reaction of the uterus could not be produced. Hohlweg (1936) commented on the large doses of prolan required to produce luteinization or corpora lutea in very young or abnormally small immature rats. Probably the important factor is the inability of the pituitary to secrete satisfactory amounts of follicle-stimulating hormone at this age. Ljachowezki and Chwatow (1937) believed that the administration of prolan in small doses (2–5 mouse-units daily) permitted successful transplantation of the ovary or testis, if injections were begun immediately after transplantation and continued for 10–12 days. They stated that such transplants could function (apparently judged by the morphology of the transplant) for more than 2 months in animals (mice, rats, guinea pigs, and cats) with their own gonads intact.

According to Desaive (1935), although repeated injections of prolan (25 rat-units daily) increase markedly the rate of development of primordial follicles, they produce an even greater rate of follicular atresia, which was considered to be the important effect in the rabbit. Moricard (1935) injected prolan for 2–5 months into rabbits. After about 3 weeks enormous numbers of corpora lutea might be found; later the predominant effect was a pronounced development of

interstitial tissue which gradually receded as "antihormone" was produced. The experiments of Bachman (1936) indicated that prolan might produce hypertrophy of the interstitial stroma or non-functional corpora lutea, if injected into young rabbits. Padootcheva and her colleagues (1935) believed that prolan is of practical value in rearing rabbits. Pregnancy was successfully initiated by causing ovulation by the injection of prolan after a suspension of spermatozoa had been injected into the uterus. The vaginal instillation of spermatazoa also was successful. The authors stated that on a rabbit farm pregnancy occurred in 74 per cent of animals receiving an ovulating dose of prolan, whereas the proportion was only 30 per cent without such treatment. The injection of prolan by various routes brings about ovulation in sheep without signs of oestrus, according to Zawadowsky and others (1935). They recommended the administration of 100–500 mouse-units and found that corpora lutea due to this treatment did not interfere with expected oestrous cycles.[8]

Comparisons of the dose of prolan necessary to cause ovulation in pregnant and non-pregnant rabbits have been made by Rowlands (1935) and are discussed on pages 69–70.[9] Prolan has some replacement value in pregnant rabbits which have undergone hypophysectomy, as was shown by Robson (1937). The same author found that, although hypophysectomy of the rabbit is followed by a rapid loss of ovarian sensitivity toward gonadotropic hormone, the injection of prolan will postpone the appearance of this refractory condition for nearly two weeks. In hypophysectomized rabbits

[8] Markee and Hinsey (1936) injected urine of pregnancy into rabbits, so that the course of ovulation could be carefully studied by observing the ovary through an abdominal window or in the anterior chamber of the eye after transplantation.

Holtz and Wöllpert (1937) used prolan to induce the formation of luteal tissue in the ovaries of guinea pigs and cats. They were interested in the uterine response to epinephrine under these conditions.

[9] Weinstein and Makepeace (1937) estimated that the dose of prolan causing ovulation in oestrous rabbits must be doubled or trebled in pseudopregnant rabbits.

also, the administration of prolan will maintain the corpora lutea of pseudopregnancy for more than a week. These effects of prolan apparently are due to its luteinizing properties; it replaces the pituitary luteinizing hormone which normally is so important for corpus luteum function and the maintenance of pregnancy. On the other hand, von Arvay (1937), who was able to prevent normal parturition and cause the prolonged retention of the dead fetuses by injecting prolan into pregnant rabbits, contended that these changes were not due to the persistent action of corpus luteum secretion.[10]

Reynolds' observations on the inhibitory action of prolan on the motility of the uterus of the unanesthetized rabbit were confirmed by Sager and Leonard (1936), who observed a similar effect following the injection of extract of urine of patients with testicular tumor or of others following gonadectomy or the menopause. The inhibitory effect could be prevented by the injection of oestrin.[11]

There are other miscellaneous observations which are difficult to classify. Vercesi and Guercio (1935) stated that the growth *in vitro* of ovarian fragments from rabbits is poor even in the presence of prolan; however, the administration of prolan for several days before ovarian removal greatly facilitates the growth of fibroblasts, which the authors considered is an important part of the response *in vivo*. According to Kiyohara and Isawa (1936), the oxygen-consumption of the isolated ovary of the guinea pig (300 gm.) is nearly doubled 10–15 hours after the injection of 7–8 cc. of urine of pregnancy. Some effect could be observed 2–3 hours after injection or as long as 10 days later. There were no similar changes in the metabolism of liver and kidney.

Hamblen in association with Ross (1937) reviewed the

[10] See also Spreng (1937) who investigated the action of a single intravenous dose of prolan on the duration of pseudopregnancy in the rat and the rabbit.

[11] Pierson (1936) produced cancer-like adenomata of the uterus in 2 of 16 rabbits by injecting a concentrated extract of pregnancy-urine on alternate days. However, it is not certain that her extract was free of oestrin.

effects of prolan in a large number of patients. In a smaller series of 7 patients, in whom ovarian specimens were available in 3 instances and endometrial samples were available in all, they found no evidence of ovulation and corpus luteum formation as a result of the injection of prolan. The authors injected total doses of 6,000–24,000 rat-units (400–8,000 rat-units daily). Among other recent descriptions of the clinical effects of prolan in women are those of Anselmino and Hoffmann (1935), Moricard (1936), and Trettenero (1936). The effects of prolan (2,000–22,000 rat-units in 4–6 days) are difficult to evaluate in the report of Anselmino and Hoffmann, because the patients all suffered from carcinoma of the uterus. Apparently the important changes were atresia of the follicles and luteinization of the thecae. Moricard transplanted the ovary into the vulva. The injection of an extract of pregnancy-urine was followed by hypertrophy of the transplant, from which oestrin-containing fluid could be aspirated. Trettenero believed that his extract of pregnancy-urine produced ovarian changes—chiefly persistence or new formation of luteal tissue in the ovaries—which modified the menstrual rhythm.

Modifications of the action of prolan may occur as a result of the injection of an oestrogen. The augmentation of the size of the corpora lutea, if an oestrogen also is administered, is probably due to the added effect of luteinizing hormone liberated from the injected animal's anterior pituitary (Wolfe, 1936; see chap. iii). It could be inferred from other data that progesterone might lessen the action of prolan. Recently, Jacobsen (1936) found that the injection of progestin (0.03–0.04 rabbit-unit daily), if made before and during the administration of prolan, markedly interfered with the formation of corpora lutea in immature mice.

In confirmation of previous work, Connon (1937) reported that large doses of prolan (80–125 rat-units daily for 3–5 days) inhibit lactation in rats, as shown by the failure of the young to grow and by the histological appearance of the

breasts. The author injected the hormone intraperitoneally from the day of delivery. The treatment caused considerable ovarian hypertrophy owing, apparently, to new formation of lutein tissue. Howard (1936) as well as Jadassohn, Uehlinger, and Zürcher (1937) observed that the injection of prolan-containing extracts caused enlargement and elongation of the nipples in rats and guinea pigs. The effects, which can also be produced by an oestrogen, were more marked in female animals. The prolonged injection of Howard's acid extract of the blood of pregnant women caused growth and differentiation of the mammary glands which often secreted milk (after injection for 90 days). The injection of the extract for 6.5–9 months was accompanied by regression of the secretory phenomena and the development of adenomata in the breasts. Howard stated that all these changes were absent in gonadectomized rats.

The effects of prolan in relation to glands of internal secretion other than the gonads. 1. *The thyroid*.—Thyroidectomy does not alter the response of the rabbit's ovary to prolan (Pitzorno and Serra, 1936: 20 rat-units on alternate days for 10 days). The same is true of the hormone's gonadotropic effect in male or female rats (Leonard, 1936; Leonard and Hansen, 1936).

2. *The adrenals*.—Several recent authors agree in their description of the effects of prolan on the adrenal glands in such mammals as the guinea pig, rabbit, rat, and mouse (Inohara, Savona, 1935; De Boissezon, 1936). The hypertrophy which occurs is limited to the cortex and has been compared with that of pregnancy. The chief alteration is in the zona fasciculata, the cells of which enlarge and contain more lipoid than usual. The zona glomerulosa may be narrowed.[12] According to Pitzorno and Serra (see above),

[12] Takewaki (1935) stated that the prolonged injection of prolan or pregnancy-urine had little effect on the adrenal of the female mouse, whereas in males it caused a disappearance of the zona reticularis with the formation of a membrane in its place.

Bau (1936) declared that pregnancy-urine, extract of corpora lutea, pars neuralis

the cortical hypertrophy due to prolan in the rabbit is prevented by thyroidectomy.

De Fremery (1934) stated that the weight of the male rat's adrenal before puberty is correlated with body-weight, whereas after puberty adrenal weight does not increase as rapidly as that of the rest of the body. (In adult female animals, adrenal weight is proportional to body-weight.) The injection of doses of prolan causing an enormous hypertrophy of the seminal vesicles did not cause any fall in the weight of the adrenals in immature male rats; as in normal immature males, there was found still to be a correlation between the weight of the body and of the adrenal glands.

3. *The thymus.*—Klein (1935–36) investigated the action of prolan on the thymus of guinea pigs. Atrophic changes were noted in both sexes. In females, however, the number of Hassal's corpuscles appeared to be increased and was accompanied by the appearance of cells described by Fulci as characteristic of the thymus of pregnant guinea pigs. Prolan did not produce such changes in male animals.

4. *The epiphysis.*—There is not acceptable evidence that pineal extract antagonizes the gonadotropic action of prolan. Vinals (1935) even believed that a suspension of beef pineal synergizes with prolan in some of its ovarian effects (see also the reports of Engel, 1936; Engel and Buño, 1936; Wade, 1937; and others).

The metabolic effects of prolan.—Prolan (20 rat-units daily for 7 days) does not alter the oxygen-consumption of albino female rats (Danforth, Greene, and Ivy, 1937). Although the administration of desiccated thyroid appeared to produce less of a calorigenic effect after the injection of oestrogens, this was not shown to be true after the injection of prolan.

Osada (1935) believed that an increased deposition of

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extract, etc., but not prolan, cause a development of the zona reticularis in the adult male mouse. In normal adult mice this zone is readily identified in females but not in males.

[135]

glycogen in the liver was the result of the injection of prolan into normal or gonadectomized rabbits of both sexes.

Creatine-creatinine metabolism in relation to age, sex, and the effect of prolan was studied in a small number of rabbits and dogs by Bühler (1935). He concluded that gonadectomy of adult animals is followed after 2–3 months by an increased urinary excretion of both creatine and creatinine. Later only the excretion of creatinine remained elevated. (Gonadectomy in immature animals did not result in such changes.) The administration of prolan was found not to affect creatine-creatinine excretion in immature dogs. In the sexually mature dog it caused a disappearance of creatine from the urine. Although prolan did not affect the urinary excretion of creatine in adult normal rabbits, it caused an increased excretion after castration. This effect could not be observed in castrated dogs. The dose of prolan used by the author in dogs or rabbits was 120 rat-units administered twice. Nitzescu and Gontzea (1937) studied creatine-creatinine metabolism in an achondroplastic, infantile dwarf. The injection of 200–300 rat-units of prolan intramuscularly brought about a reduction in the excretion of creatine but scarcely affected that of creatinine. Also there appeared to be an increased creatine-tolerance. The same phenomena were more pronounced following the administration of male hormone (4 capon-units of "Erugon").

The effects of prolan on the metabolism of only one lipoid, cholesterol,[13] have been investigated recently. Szpidbaum (1935) found that the blood-cholesterol rose (e.g., 40–50 per cent or more) after the injection of prolan into patients recovering from typhoid fever. He believed that the hormone caused a mobilization of cholesterol reserves with consequent benefit to patients because of an increased non-specific immunity. Szpidbaum injected total doses of 1,500–3,000 rat-units as 500 rat-units daily or on alternate days. Other observations have all been made in rabbits (Cioglia, 1935–36;

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[13] Presumably all the authors determined the total cholesterol.

Teilum, 1936; and Tramontana, 1936). There was observed consistently a hypercholesterolemia following the injection of prolan. Cioglia concluded that hypercholesterolemia of early pregnancy is due to prolan, whereas the reduced or abnormally low concentration of the lipoid in later pregnancy depends upon the effect of an oestrogen.

Two reports deal with the action of prolan on the concentration of inorganic substances in the blood. According to Klodt (1937), the subcutaneous administration of prolan to rabbits (500 rat-units daily for 6 days) brings about a transient rise in the concentration of Na associated with a fall of K and inorganic P. Less water and Na are excreted by the kidneys. In the other report Dell'Acqua (1935) confirmed Cannavó's statement that prolan causes a rise in the concentration of Mg in the blood. The average increase was 38 per cent (20–78 per cent; 6 experiments in 2 cats).

Marchesi (1935) reported that female rats on a diet free from vitamin E, and otherwise sterile, could become pregnant (by normal males) following the administration of prolan. The young died shortly after birth, because of the absence of lactation. A glycerol extract of the placenta was even more effective than prolan. Van Os (1936) studied the effect of prolan on the degenerated testis of the rat on a vitamin-A-free diet. The interstitial cells were stimulated, but there was not resumption of spermatogenesis.

The growth of neoplasms in relation to prolan.—Prolan appears not to have important inhibitory effects on the growth of neoplasms. Magath and Smoilowskaia (1935) concluded that the injection of 50–100 rat-units daily for as long as a month might cause a maximum inhibition of 50 per cent in the growth of a neoplasm. These investigators used mice and rats (transplanted mammary adenocarcinoma and Jensen sarcoma). Other reports of Bischoff and Maxwell, Druckrey, Engel, and Katz are discussed in chapters ii and iii.

Miscellaneous observations.—Prolan does not affect the coagulation-time of the blood in man (125–250 rat-units

daily for 9–20 days; Chew and others, 1935). Nicolle (1936) concluded that the hormone causes a reticulocytosis in the rabbit, whereas oestrone has the opposite effect. In the rabbit, also, Wilson (1937) observed a marked leukocytosis in normal female rabbits 5–8 hours after injection. Repeated injections did not produce this effect. Wilson was not convinced that this was a specific effect.

Prolan appears not to be of value in the treatment of acne vulgaris (total dose about 5,700 rat-units over 8–11 weeks; Williams and Nomland, 1937). Moffat (1937) believed that small doses of prolan may cure "menstrual migraine"; however, he gave no evidence that such treatment is of specific importance. According to Steinbach and Klein (1937), experimental tuberculosis caused by a standardized dose of bovine bacilli in guinea pigs takes a much less severe course, if extract containing prolan or pregnant-mare serum be injected repeatedly. A similar effect could not be observed following the administration of anterior pituitary extract.

The contractile activity of the isolated ureter of the pig is not affected by the addition of 500 rat-units of prolan to 150 cc. of bath fluid (Schmitz, 1937).

The experimental augmentation or inhibition of the gonadotropic effects of prolan. 1. Augmentation.—It is well known that gonadotropic extracts of the pituitary (or probably derived from the pituitary as in the urine of spayed women) may enormously enhance the gonadotropic action of prolan, as indicated by hypertrophy of the ovary of the immature rodent. Probably the follicle-stimulating component of such extracts is reponsible for this synergism. The luteinizing effects of prolan can be manifested to a maximum extent, if the ovaries are properly prepared by widespread growth of follicles. Non-specific augmentation, as with $ZnSO_4$, usually cannot be demonstrated if prolan instead of anterior pituitary extract is used as the gonadotropic agent.[14]

[14] For an apparent exception see Emery (1937).

2. *Inhibition.*—The administration of certain anterior pituitary extracts may inhibit the gonad-stimulating effect of prolan. This phenomenon is best observed after the intraperitoneal administration of the anterior pituitary extract. The mechanism of this inhibitory action is not known; the obvious possibility that a local action on the ovary is important has not been investigated.

The doctrine of antihormones as related to prolan.[15]—The degree of purity of the best preparations of prolan is not known. Like similarly impure anterior pituitary extracts, preparations of prolan, if repeatedly administered for weeks or longer, produce progressively reduced gonadotropic effects until the organ affected—whether ovary or testis—is refractory to further treatment. "Antihormone" or a substance inhibiting the action of the extract in fresh, non-injected animals can be detected in the serum at this time. Its site of formation may be the reticulo-endothelial system.[16] Are these phenomena important physiologically? Probably not. The chorionic epithelium of the placenta of women secretes enormous quantities of prolan into the blood throughout pregnancy, although the peak of formation suddenly appears at about the end of the second lunar month. There is no evidence of any formation of antihormone by the tissues of pregnant women. It appears that the numerous investigations of the formation and characteristics of prolan-antihormone represent, at most, contributions to a new field of immunology.

Eichbaum and Kindermann (1935) and Kindermann and Eichbaum (1936) have published several communications on

[15] Other experiments in which prolan was used are discussed in chap. iii (pp. 110 ff.).

[16] Experiments of Gordon, Kleinberg, and Charipper (1937) in splenectomized rats to some of which trypan blue was also administered to "block" the reticuloendothelial system. The refractory (non-responsive) condition of the ovary appeared much later in splenectomized rats also receiving trypan blue. Ten rat-units of prolan were injected daily. When refractoriness of the ovary finally appeared, it was attributed to the production of antihormone by redeveloped reticulo-endothelial tissue.

the immune aspects of antihormone due to prolan prepared from urine of pregnancy. They found that the apparent concentration of antihormone present in the serum of rabbits could not be correlated with precipitin or complement-deviation reactions. Such immune reactions appeared to depend upon (1) an antibody specific for human protein and (2) an antibody specific for an antigen associated with prolan but occurring in human urine irrespective of the presence or absence of prolan. The results of Bachman (1935), although less complete, are in agreement with those of Kindermann and Eichbaum. Twombly (1936) favored the view that antihormone toward prolan is similar to an antibody formed in response to a foreign protein. The precipitin-reaction (rabbits were given an extract of pregnancy-urine) was parallel to the antihormone content of sera. Prolan inactivated because of heat or age was about as efficient in evoking antihormone formation as were potent preparations. The serum of patients receiving prolan (100 rat-units daily) for 2–6 weeks or for more than a year contained no antihormone—indicating that the protein, being homologous, evoked no antibody reaction. In confirmation of Twombly, De Fremery and Scheygrond (1937) reported that an extract of male urine, if injected into rabbits, caused the production of substances preventing the gonadotropic effects of prolan. It seemed unlikely that the small amount of gonadotropic activity in the "antigen" could be responsible for the effect. The urine contained non-specific substances with the antigenic properties of prolan.[17]

Harington and Rowlands (1937) investigated the chemical nature of gonadotropic antihormone in the serum of the goat or the rabbit which had received repeated injections of prolan or extract of pregnant-mare serum. The antihormone of prolan was recovered quantitatively in the globulin fraction of serum and was distributed between the pseudoglobulin

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[17] See also Laroche and Simmonet (1936) who injected "Antélobine" into patients and subsequently tested their serum for antihormone.

and euglobulin fractions. The antihormone inhibiting the action of the extract of pregnant-mare serum could not be completely recovered; most of it appeared also to be associated with the globulin fraction of serum. Zondek and Sulman (1937) have published several reports on biochemical reactions between prolan and its antihormone. They concluded that the antihormone is similar to an antibody. The reaction between prolan and its antibody is reversible.[18] The authors were unable to detect antihormone in tissues (liver, spleen, muscle) or in the urine of animals whose serum contained the substance. Biochemical differences between prolan and its antihormone were also described.[19]

The assay of prolan.[20]—The remarks which were made in chapter iii in reference to the assay of pituitary gonadotropic hormone apply with equal force to prolan. As soon as suitable standards have been assayed by different technics and the results evaluated, it will be possible to recommend preferred assay technics. Among reports published recently are those of Davy (1935), Korenchevsky, Dennison, and Simpson (1935), Owen (1936), Morosowa (1936), and Kelly and Woods (1937). Nelson and Overholser (1935), basing their results on various criteria—i.e., opening of vaginal orifice, oestrus, ovulation, follicular stimulation, luteinization— estimated the relationship between the mouse-unit and the rat-unit for several gonadotropic hormones to be as given in Table 3. Their belief in the remarkable lack of potency of prolan in the mouse as compared with the rat is in agreement with most of the older reports.

Levin and Tyndale (1937) found that the increase of uter-

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[18] In one report the authors state that the antihormone destroys prolan.

[19] Zondek and Sulman also studied biological effects of the antihormone of prolan. Antihormone produced no effect after administration by way of the gastrointestinal tract. After subcutaneous injection, antihormone could be retained in the body for several days. Also it could inhibit the effect of prolan, if injected 24 hours after the hormone was administered. They regarded it as being both species and organ specific (it did not antagonize the gonadotropic action of extract of blood of pregnant women or of extract of the human anterior pituitary).

[20] See also chap. iii.

[141]

ine weight in the immature rat, although suitable for the biological estimation of pituitary follicle-stimulating hormone, cannot be used for the accurate assay of prolan or the active principle of pregnant-mare serum.

The chemistry of prolan.—Prolan has not been prepared as a pure substance. There is not good additional evidence that it is composed of more than one gonadotropic principle, although Brindeau, Hinglais, and Hinglais (1936) contend that it is a mixture of 3 principles. Reports of the hormone's preparation by modifications of the tannic acid, tungstic acid, or benzoic acid methods as applied to urine have been made by Hellbaum, Fevold, and Hisaw (1935), Freud and Hechter (1936), and Ito, Hajazu, and Ueno (1936). Also, Fevold and

TABLE 3

GONADOTROPIC EXTRACT OF	RELATIVE DOSE FOR ONE UNIT IN	
	Mouse	Rat
Pregnancy-urine..................	5	1
Sheep pituitary..................	1	3
Pregnant-mare serum............	1	2

Hisaw (1936) described a method based on the extraction of the hormone from urine by means of 10 per cent cresol. The effect of hydrogen-ion concentration,[21] various organic reagents, etc., on the hormone has been studied by Bischoff and Long (1936).

GONADOTROPIC HORMONES ASSOCIATED WITH NEOPLASMS IN MAN

The neoplasms with which the excretion of large quantities of what is probably prolan are most definitely associated are hydatidiform mole and chorionepithelioma. Malignant testicular neoplasms likewise may produce large quantities of prolan-like hormone which, however, may differ from pro-

[21] See also Elden and Fellows (1935).

lan in important aspects of its action (see the earlier volume). Blümel (1935) emphasized the diagnostic significance of the presence of considerable quantities of gonadotropic hormone in the urine. However, cerebral disease with increased intra-cranial tension as well as the disappearance of internal secretory activity by the gonads, as after the menopause, must be ruled out, because these conditions may give rise to the excretion of gonadotropic hormone in quantities greater than normal. Search should then be made for hydatidiform mole, chorionepithelioma, or teratoma. The last-named tumors may, of course, also occur in males. Provided the neoplasm secretes gonadotropic hormone, determinations of the latter during treatment have obvious prognostic significance.

Testicular tumors in relation to hormone-excretion have been recently discussed by Freed and Coppack (1935), Zondek (1937), and Hinman and Powell (1938). Fifty-eight patients with testicular neoplasms were investigated by Hinman and Powell. The greatest amount of hormone was excreted by patients with teratoid chorionepithelioma of the testis (20,000 to 3,000,000 mouse-units per liter of urine). Large amounts might be secreted by teratoid adenocarcinomata, by "differentiated" (partly carcinomatous) teratoid neoplasms or by primitive monocellular carcinomata. Only small amounts of hormone were excreted by the large number of patients with differentiated monocellular carcinoma of the testis. No hormone could be found in the urine of patients with dysgerminoma (Zondek) or "adult" tumors classified as adult teratoma or adult seminoma (Hinman and Powell). Benign hypertrophy and carcinoma of the prostate or hyper-nephroma do not secrete gonadotropic hormone, as indicated by its absence in the urine of patients (Owen and Cutler, 1936).[22]

So-called prolan A or B may be found in women with genital carcinoma other than the tumors already discussed. It has not been shown that such hormone is not secreted by

[22] See also Aron (1935) and Baudler (1936).

the pars glandularis. Baudler (1935–36) in recent reports associates such findings with destructive malignant tumors such as carcinoma of the cervix, vulva, or ovary. Sometimes the same is true of extragenital malignant tumors of men or women. It must be remembered that the tumor itself or radiation therapy of such tumors might interfere with the secretion of male or female hormone by the gonads, so that the increased excretion of gonadotropic hormone could resemble that following gonadectomy.

Lewis and Geschickter (1936) investigated the concentration of gonadotropic hormone in various tumors. Some of the results, expressed as rat-units per kilogram tumor, were as follows: breast tumors—carcinoma (5 negative), 6,000–7,000 rat-units, fibromyxoma, 60,000 rat-units, fibroadenoma, 2,500 rat-units; uterine myomata (2 negative), 4,500–11,000 rat-units; irradiated sclerosing osteogenic sarcoma, 4,500 rat-units.

THE GONADOTROPIC HORMONE OF PREGNANT-MARE SERUM[23]

In several respects, the gonadotropic hormone of the serum of the pregnant mare is strikingly different from prolan. Considerable quantities are present in the serum only during a limited part of the gestation period. It is not excreted in significant amounts in the urine even at times when its concentration is highest in the serum. It can produce marked stimulation of the gonads of birds, whereas prolan is without action in this class of animals. As might be inferred from its failure to appear in the urine, it is slowly metabolized, so that the administration of a single dose, during a period of several days, may be as effective as repeated doses. It apparently can replace the gonadotropic hormones no longer secreted because of hypophysectomy, at times when prolan is patently inadequate. It produces unquestionable follicle-stimulating effects, whereas prolan does not.

[23] See the Index for references to other reports.

Methods of securing purified hormone have been described lately by Evans and others (1936), Gustus, Meyer, and Woods (1936), and Cartland and Nelson (1937). Gustus, Meyer, and Woods adsorbed the hormone on a suspension of $Al(OH)_3$ from which elution was accomplished by means of dilute NH_4OH. Cartland and Nelson not only described in detail a method of making very potent extracts but also studied some of the hormone's properties. It was found to be soluble in serum containing 50 per cent acetone or 60 per cent ethanol. When the percentage of acetone or alcohol was raised to 70 per cent (pH 6) the greater part of the gonadotropic substance was precipitated. Further manipulation permitted the isolation of preparations of a potency of 0.05 mg. for each rat-unit. (In terms of ovarian effect, their rat-unit was 2–10 times as potent as that used by others.) The hormone could be inactivated by HCHO (4 per cent, pH 8.0, 3 hours) or heat at 70° C. or above. Inactivation by heat was studied at three hydrogen-ion concentrations: pH 6.0, 7.0, and 8.0. Destruction, especially at 70° C., was greatest at pH 6.0 and least at pH 8.0. Enzymic destruction took place in the presence of trypsin (also reported by others), but not in the presence of emulsin or invertin. The high concentration of hydrogen ions necessary for investigating the effect of pepsin produced inactivation in the absence of the enzyme.

The investigation of Evans and his colleagues is of interest because of their finding that suitable concentrations of $(NH_4)_2SO_4$ can be used to fractionate pregnant-mare serum into two components, one chiefly stimulating follicle-growth and the other causing a "hypertrophy of the theca interna and interstitial tissue" without follicle growth or the formation of lutein tissue. The second fraction restored the function of the interstitial cells of hypophysectomized rats. The follicle-stimulating fraction apparently was not free from the second principle; its action in male rats after hypophysectomy was not described. Hellbaum (1937) declared that follicle-stimulating, luteinizing, and augmenting substances can

be separated by suitable methods; however, his views have been given only in the form of an abstract. Although Cole earlier believed that more than one gonadotropic principle is present in pregnant-mare serum (e.g., Saunders and Cole, 1935), he later reported (1936) that he was unable to confirm this belief. Also, Cartland and Nelson at no time secured evidence of the presence of more than a single principle. For purposes of discussion it will be assumed that there is but one gonadotropic principle, although new work may support the belief that a mixture of principles really is secreted.

The slow metabolism of the hormone and the failure of the kidneys to secrete appreciable amounts have already been mentioned. In this connection the experiments of Catchpole, Cole, and Pearson (1935) are of interest. The authors found that about 50 per cent of the hormone disappeared from the rabbit's blood 26 hours after intravenous injection (see Fig. 19). In the gelding the same proportion disappeared in 6 days. The hormone probably was destroyed, inasmuch as none could be found in the urine or feces or in tissues such as the uterus, lungs, kidneys, spleen, or liver. The rate of destruction was not affected by gonadectomy.

Extract of the serum of pregnant mares stimulates the gonads of male or female fowls.[24] In the immature cockerel the homone causes testicular hypertrophy (without precocious spermatogenesis) and a marked growth of the comb.[25] In immature females there is only moderate hypertrophy of the ovary without ovulation but with marked growth of the oviduct; the head furnishings are female in type.

Cole (1936) as well as Hamburger (1936) investigated the action of the hormone in both sexes of several species of mam-

[24] Recent reports are those of Asmundson and Wolfe (1935), Hamburger (1936), Uhl, Engelbreth-Holm, and Rothe-Meyer (1937), and Zavadowsky and others (1937).

[25] The cockerels used by Zavadowsky and his colleagues were 50 days old. Injections of 50–200 mouse-units of the hormone for 20–40 days produced tremendous comb growth, testicular hypertrophy, and spermatogenesis. Regression and even degenerative changes appeared after long-continued administration of the hormone.

mals.[26] Saunders and Cole (1936) showed that only the ovarian interstitial tissue is stimulated in rats 10–15 days old, whereas follicular stimulation was marked in animals 18 days
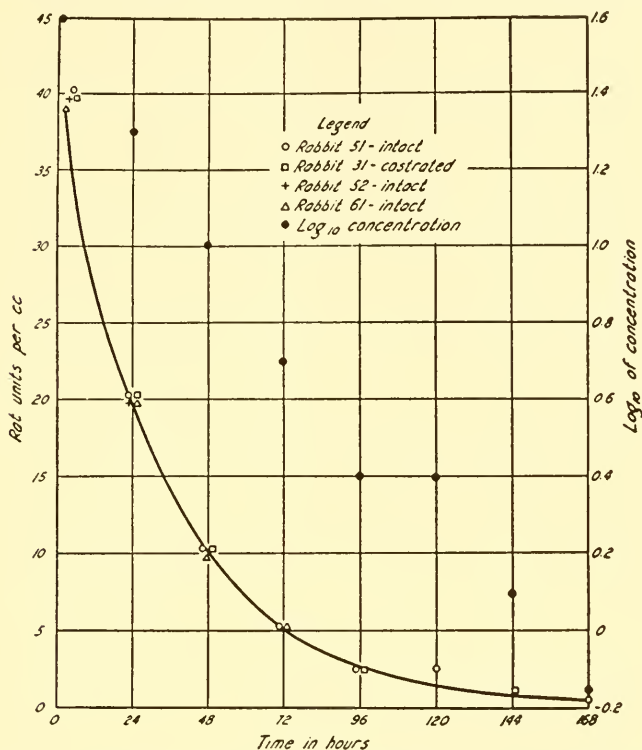
FIG. 19.—The rate of disappearance of the gonadotropic hormone of pregnant-mare serum following the intravenous injection of 3,000 rat-units into rabbits. (From Catchpole, Cole, and Pearson, Amer. J. Physiol., **112**, 21–26 [1935].)

old, and ovulation and corpus luteum formation appeared with increasing frequency in still older rats (19–25 days old.)[27]

[26] Wells (1937) describes the action of the hormone in a hermaphrodite ground squirrel.

Engel (1936) and Engel and Buño (1936) believed that certain pineal extracts antagonize the gonadotropic action of the hormone.

[27] None of the rats was hypophysectomized. However, others, including Hamburger, have observed the formation of lutein tissue in hypophysectomized rats receiving an extract of pregnant-mare serum.

Cole was able to produce ovulation in the rat, ewe, cow, and sow. Both Cole and Hamburger agree that the seminiferous tubules and interstitial cells are affected in male rats; however, the greater effect is on the interstitial cells. The hypertrophy of the testis in relation to that of accessory sexual organs is greater after pregnant-mare serum than after prolan; however, anterior pituitary extract excels both in this respect (Leonard and Hansen, 1936). The same authors found that the action of pregnant-mare serum is not altered after thyroidectomy.

Cole (1937) reported that the injection of the hormone into adult female rats at a suitable time (12 rat-units during metoestrus) was followed by pregnancies resulting in an increased percentage of large litters. Matings occurred in about half of a series of immature rats receiving daily injections when 26–31 days old. At necropsy about the 10–12 day of pregnancy, more than 20 implanted fetuses could be counted in 38 per cent of the immature rats. There were 17 young in the largest litter born alive. The percentage of fertile matings in immature or adult rats was reduced by large doses of the hormone.

SUMMARY

Large quantities of gonadotropic hormone may be liberated into the blood stream during pregnancy in man and other primates and in the mare. Presumably, such hormone is important in insuring the maintenance of pregnancy which, especially at first, requires adequate amounts of the internal secretion of the corpus luteum of the ovary. The corpus luteum in turn cannot flourish unless it is furnished with "luteinizing" gonadotropic hormone either by the anterior pituitary or by some other organ. In some animals, for at least part of the period of gestation, the anterior pituitary appears to supply most of the gonadotropic hormone required. In man, however, the chorionic epithelium of the placenta furnishes enormous quantities of luteinizing hormone (pro-

lan), especially toward the end of the second lunar month, and thus possibly replaces the anterior pituitary. When gestation is completed or fails because of fetal death, this hormone is no longer secreted, either because the placenta, together with the other products of gestation, leaves the body or because the placenta degenerates and is resorbed or removed.

Conditions in the pregnant mare appear to be different, although the function of the gonadotropic hormone probably is similar. The period of secretion is more sharply limited (especially between the 40–80 days of gestation). The endometrium as well as the chorionic epithelium secretes a hormone which is far more complete in its gonadotropic effects than is prolan. Whereas prolan is chiefly a hormone facilitating the growth and function of lutein tissue in the ovary or of the interstitial cells in the testis, the gonadotropic principle(s) of pregnant-mare serum resembles anterior pituitary gonadotropic principles in respect of the adequacy and completeness of its effects. The chorionic-endometrial hormone of the pregnant mare can maintain the gonads of hypophysectomized male or female animals and therefore affects the follicles, corpora lutea, and interstitial tissue of the ovary or the interstitial cells and germinal epithelium of the testis. Likewise this hormone stimulates the gonads of birds, whereas prolan does not. Some believe that the hormone is a mixture of gonadotropic principles. However, more evidence is needed before this belief can be accepted. On the other hand, prolan appears to be a single gonadotropic substance.

In this chapter and in others which have preceded it, the recent investigations of the effects of these hormones characteristic of pregnancy are discussed. Neither hormone has been isolated as a pure substance. If either is injected repeatedly, the gonadotropic effects disappear, and an associated production of "antihormone," which can be found in the globulin fraction of serum, takes place. The hormone of pregnant-mare serum appears to have much the greater

promise as a therapeutic agent, both because its gonadotropic effects are nearly complete and because it is remarkably slowly metabolized, apparently not being excreted but only undergoing a slow destruction.

Gonadotropic hormone can be found in certain neoplasms in man such as hydatidiform mole, chorionepithelioma, certain malignant tumors of the testis (especially teratoid neoplasms),[28] and in some extragenital tumors (e.g., sarcoma of breast or bone). Urinary excretion of hormone may be marked in patients with hydatidiform mole, chorionepithelioma, or testicular tumor; its course in relation to treatment may furnish information of great value with respect to prognosis. The excreted gonadotropic hormones may be different—that of chorionepithelioma or hydatidiform mole resembles the prolan of normal pregnancy, whereas those associated with testicular neoplasms may have different or additional biological effects.

It has not been shown that the moderate quantities of gonadotropic hormone excreted by women with other types of carcinoma of the genital tract do not arise in the anterior pituitary.

[28] The absence of gonadotropic hormone in the urine does not indicate that a testicular tumor is not malignant.

CHAPTER V

THE PARS GLANDULARIS OF THE PITUITARY BODY IN RELATION TO THE DEVELOPMENT OF THE BREASTS AND THE SECRETION OF MILK[1]

THE relationship between lactation and the secretory activity of the pars glandularis is complex and only incompletely understood.[2] It is agreed that the lactogenic hormone initiates and maintains lactation. However, its presence in adequate concentration in the blood is a necessary but not a sufficient condition of lactation. Moreover, preceding lactation there must be proper development of the mammary glands. The extent to which this prelactation growth depends either directly on an internal secretion of the pars glandularis or indirectly on gonadotropic hormones which increase gonadal function is still a problem undergoing active investigation.

Lactation cannot continue in the absence of the pituitary body. The correctness of this statement which has been generally held for some years was recently again confirmed in the guinea pig (Gomez and Turner, 1936; Macchiarulo, 1936) and in the dog (Houssay, 1935). The other aspect of this discovery is represented by the following question: After hypophysectomy in a lactating animal, can lactation be maintained by the lactogenic hormone alone, or are several anterior pituitary hormones required? In the pigeon, according to Schooley, Riddle, and Bates (1937), proliferation of the crop-glands and the formation of crop-milk, which are changes homologous to breast development and lactation in

[1] The pars neuralis, pars intermedia, and pars tuberalis have not been shown to be of significance.

[2] See also reviews of other work in chaps. iii and iv.

[151]

mammals, can be produced by the injection of lactogenic hormone into hypophysectomized birds. The authors mention that the response to this hormone in hypophysectomized rabbits is a small fraction (about one-eighth) of that in normal rabbits. Other authors agree that the lactogenic hormone, by itself, can neither initiate nor maintain lactation in hypophysectomized mammals, although the breasts may appear to be fully prepared for stimulation or continuance of stimulation. It appears that the initiation or continuance of lactation requires at least two hormones of the pars glandularis—the lactogenic hormone and the hormone stimulating the adrenal cortex ("corticotropic" hormone). Some authors would further lengthen the list, especially with respect to a separate action of the anterior pituitary on carbohydrate metabolism. The importance of all these factors will be considered after the conditions necessary for breast development prior to lactation have been discussed.

THE INFLUENCE OF THE ANTERIOR PITUITARY ON THE DEVELOPMENT OF THE BREASTS PRIOR TO LACTATION

Before lactation can occur, there must be suitable development of the breasts. Such development cannot occur in hypophysectomized animals, probably because of two factors: (1) any favorable influence of the gonad will be prevented by the lack of gonadotropic hormone, and (2) the anterior pituitary appears to secrete a hormone essential for mammary development, even when the latter follows the administration of an oestrogen.

The development of the mammary gland in relation to oestrogens.[3]—In a mammal like the rabbit the repeated injection of an oestrogen such as oestrone may cause a marked development of the mammary tree, especially of the ducts. The

[3] Debré, Marie, and Bernard (1935) described marked development of the breasts in a girl eight years of age without any other signs of puberty. The development of the vulva and bones corresponded to the child's age. There had been no uterine bleeding.

growth of alveoli appears to depend to an important extent on the action of progesterone, although this may not be true of other mammals, e.g., the guinea pig. Gardner, Gomez, and Turner (1935) produced mammary development in normal male rabbits or in normal or spayed (multiparous) female rabbits by injecting 20–25 rat-units of oestrone daily for about 3 weeks. If lactogenic hormone was injected within not more than 3 days after oestrone treatment was stopped, lactation promptly appeared. The observations of others who used rabbits do not require a detailed description.[4] Similar experiments have been performed in castrated male rabbits. In the normal monkey (Allen, Gardner, and Hill, 1935) and in the goat (De Fremery, 1936) the administration of an oestrogen will likewise suitably prepare the mammary gland so that lactogenic hormone is then effective. Gardner (1935) produced general development of the duct system, as well as some localized growth of alveoli in male mice with ovarian grafts in the testis. In the depancreatized bitch treated with insulin, lactogenic hormone produces lactation, provided that mammary development corresponds to that of pregnancy or pseudopregnancy (Nelson, Himwich, and Fazekas, 1936). Houssay (1935) used only an oestrogen to bring about mammary development in normal or gonadectomized dogs of both sexes ("folliculin" as 1,000–10,000 international units daily for 49–90 days). The intraperitoneal administration of what was probably a crude extract of beef anterior lobe then caused lactation.[5]

Certain experiments in the mouse, rat, and guinea pig are of particular interest because they indicate that mammary development following the administration of an oestrogen cannot take place in the absence of the pituitary body.[6]

[4] Anselmino, Herold, and Hoffmann (1935), Macdonald (1936), Margulis (1936), Pallot (1936), and Gillard (1937).

[5] The effects were present after removal of the lumbar sympathetic chains.

[6] Houssay stated that the pituitary is not necessary in the dog. Nelson (1935) reported that oestrone produced about the same degree of mammary development in male guinea pigs, whether or not the pituitary had been removed. Also, Asdell and

Gomez, Turner, Gardner, and Hill (1937) observed no development of the rudimentary mammary glands in completely hypophysectomized male mice receiving injections of various oestrogens (50–500 international units weekly). If, however, a very minute fragment of the pars glandularis remained, the injection of oestrogen brought about mammary growth and development. Likewise in male or female rats oestradiol benzoate will cause no growth of the breasts after hypophysectomy, although this action is not prevented by gonadectomy (Reece, Turner, and Hill, 1936). Atrophy of the mammary glands due to the removal of the pituitary from the rat cannot be halted by oestrone; however, inanition seems to be an important factor (Astwood, Geschickter, and Rausch, 1937). Other experiments by Gomez and Turner (1936), who used guinea pigs, also lead to the conclusion that growth and development of the mammary ducts and parenchyma following the injection of moderate to enormous doses of oestrone or oestradiol benzoate (e.g., 25–1,000 international units daily) cannot take place after hypophysectomy has been performed.[7] If, however, hypophysectomized male guinea pigs receive implants of the pituitary of male rats in which breast development has been induced by injections of oestrone, growth of the nipples and breasts including the development of alveoli occurs, whereas implants from rats to which no oestrone has been given do not affect the recipient guinea pig's rudimentary nipples and breasts (Gomez, Turner, and Reece, 1937). According to Robson (1936), little or no development of the mammary glands occurs in rabbits hypophysectomized about the 22–24 day of pregnancy de-

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Seidenstein (1935) found that oestrone in combination with progestin caused about equally good development of the mammary glands in spayed rabbits with an intact pituitary or after partial or complete hypophysectomy. Do these findings indicate that the animals used were not completely hypophysectomized? According to Gomez and others (1937), remnants of the anterior pituitary, too small to maintain the gonads or the adrenals, permit the response of the mammary gland of the mouse to an oestrogen.

[7] The growth of the nipple due to administered oestrogen is not affected by hypophysectomy (Gomez and Turner, 1936).

spite the injection of progestin or progesterone to term. Gomez and Turner (1938) suggest that a pituitary "mammogenic" hormone is secreted in response to an oestrogen or to an oestrogen and progesterone and that this hormone, perhaps made up of two components, brings about the growth of the mammary ducts and the development of the lobules and their alveoli. The authors injected simple preparations of the anterior pituitary of pregnant or non-pregnant heifers into a small number of rats and rabbits which had been spayed when immature. The administration of anterior pituitary from non-pregnant heifers—although lactogenic hormone was present in the injected anterior pituitary—did not affect the mammary gland. On the other hand, if anterior pituitary of pregnant heifers was injected for several weeks, mammary development corresponding to advanced pseudopregnancy or pregnancy could be produced both in rabbits and rats.

These results indicate that the growth and development of the breasts are as dependent upon the pars glandularis as lactation itself. A complex interplay of the hormones of the anterior pituitary and the ovary may take place normally. Gonadotropic hormone secreted by the anterior pituitary maintains ovarian function, whence arises the secretion of oestrogen and progesterone. In non-pregnant animals oestrogen chiefly causes the formation and liberation of a substance from the anterior pituitary, so that partial growth and development of the breasts occur. In pregnant animals the production of "mammogenic" hormone(s) is increased further not only by the increased quantities of oestrogen produced in the ovaries and placenta but also by the added stimulation afforded by the prolonged secretion of corpus luteum hormone. As a result, full development of the breasts preparatory to lactation occurs. The lactogenic hormone of the anterior pituitary then initiates the secretion of milk.

Progesterone as a factor in the development of the mammary glands.—Progesterone, the secretion of the corpus luteum, is

believed to vary in significance as a cause of breast development. Certainly, it is much less important than oestrogen and is thought to act only after some growth, especially of the ducts, has already occurred, following the secretion or administration of oestrogen. Most authors have concluded that the secretion of the corpus luteum is of definite importance in bringing about alveolar development in the rabbit's breast, provided that growth of the ducts has been stimulated by oestrogenic hormone.[8] Lactogenic hormone then readily produces or "releases" the secretion of milk. On the other hand, in the guinea pig and rat, progesterone appears to be of little significance in supplementing the effects of oestrogens on mammary growth and development (Gardner and others, 1935; Repetti, 1936; Astwood and others, 1937; and Nelson, 1937).[9]

The effect of androgens on the development of the mammary glands.—As in female rats, the post-pubertal development of the breasts in male animals is prevented by gonadectomy. Testosterone propionate, although without oestrogenic effects, will cause mammary development in spayed rats (McEuen, Selye, and Collip, 1936). The authors injected 3 mg. of testosterone propionate as the total dose over 11 days. Astwood, Geschickter, and Rausch (1937) concluded that testosterone can bring about, in young male rats, mammary development corresponding to that in adult males. Large doses of the hormone, although causing cyst formation and an increase in the fibrous tissue, produced no development of the mammary tree such as followed the administration of oestrone. Apparently the effects of testosterone on the breast, like those of an oestrogen, are secondary to the secretion of an anterior pituitary hormone; hypophysectomy prevents such effects (McEuen, Selye, and Collip, 1937).

[8] Gardner, Gomez, and Turner (1935); Anselmino, Herold, and Hoffmann (1935); Macdonald, Pallot (1936); Gillard (1937).

[9] Such observations should be made in spayed animals, inasmuch as the oestrogen may bring about the new formation of lutein tissue by increasing the rate of liberation of luteinizing hormone from the anterior pituitary.
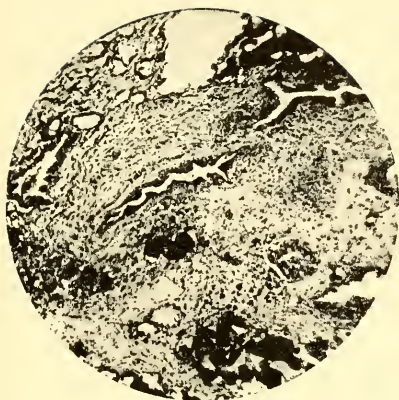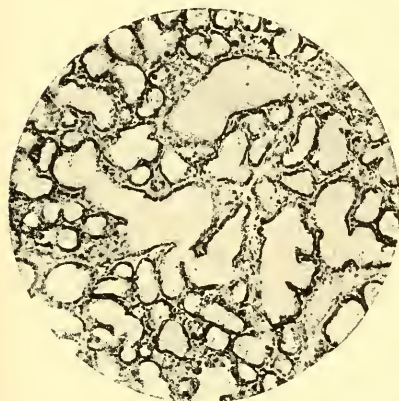
Fig. 20.—Photomicrographs of biopsy specimens of breast from a single castrated male rabbit. (From Anselmino, Herold, and Hoffmann, Zbl. Gynäkol., **59,** 963–69 [1935]) *A*, After castration. *B*, After treatment for 25 days with oestrogen. Development of the ducts has taken place. *C*, After further treatment for 6 days with corpus luteum hormone. There is marked development of the alveoli. *D*, After the administration of anterior pituitary extract (lactogenic hormone) for 5 days. Lactation is under way.
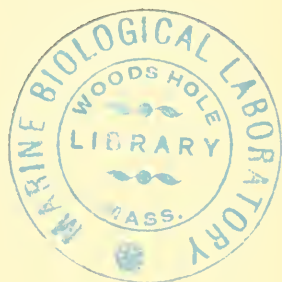
The effects of various hormones on the morphology of the breast are well illustrated by figures reproduced from a report by Anselmino, Herold, and Hoffmann (1935). All the samples of breast tissue were removed from the same castrated male rabbit after castration (Fig. 20, *A*) and after treatment for nearly 4 weeks with oestrin (Fig. 20, *B*), followed by the daily injection of progesterone for 6 days (Fig. 20, *C*). Finally, extract containing anterior pituitary lactogenic hormone was administered for 5 days; lactation then appeared (Fig. 20, *D*).

THE LACTOGENIC HORMONE[10]

Provided that there is adequate development of the breasts, the secretion of milk in normal mammals probably takes place because of the release and continued secretion of the lactogenic hormone of the anterior pituitary. However, this statement is not meant to exclude the participation of other hormones, including, particularly, the adrenal cortical hormone. After hypophysectomy, with which is associated a marked reduction of the activity of the rest of the endocrine system, lactogenic hormone alone will not initiate or support lactation, although the breasts may be suitably developed or secreting milk at the time of operation.

It is now proposed to discuss factors which influence, both positively and negatively, the action or the conditions necessary for the action of the lactogenic hormone.

The effect of suckling on the secretion of lactogenic hormone.— Selye, Collip, and Thomson had earlier demonstrated that the stimulus of suckling, without the escape of milk, maintains the secretion of lactogenic hormone, as shown by lactation in breasts from which the nipples had been excised.[11] Ingelbrecht's experiments (1935) indicate that the reflex

[10] Synonymous terms are galactin, mammotropic hormone, and prolactin.

[11] In the guinea pig, unlike the rat, ligation of the galactophores is rapidly followed by failure of lactation in the corresponding breast, although suckling and lactation continue in the other breast with a normal nipple (Hesselberg and Loeb, 1937).

stimulation of the release of lactogenic hormone from the pars glandularis is prevented by section of the spinal cord. The author severed the spinal cord between the last thoracic and first lumbar segments in lactating rats and covered the 6 upper nipples, which were still sensitive, with tape. Despite vigorous suckling of the insensitive nipples, the young died within 48 hours. However, if only two sensitive nipples were left exposed or if a hemisection of the spinal cord was performed, lactation continued in the breasts of the anesthetized and paralyzed abdomen. Reece and Turner (1936) investigated the effect of suckling and removal of the secreted milk on the amount of lactogenic hormone in the pituitary of lactating rats. In terms of pigeon-units, the results obtained in one set of observations are given in Table 4. Thus, it ap-

TABLE 4

Units per Gland

1. Normal suckling..................................... 7.7
2. Accumulation of milk without suckling for 15 hours. 9.2
3. No suckling for 12 hours followed by suckling for 3 hours... 3.1
4. Suckling (as in 3) but without removal of milk due to ligation of main galactophores................. 5.2

pears that suckling causes a marked release of stored lactogenic hormone and that the removal of accumulated milk may be an additional factor.

Lactogenic hormone as a factor in promoting the secretion of milk in hypophysectomized animals.—It is well known that lactation promptly ceases after the pituitary body has been removed from lactating animals. For the restoration of lactation in such animals the lactogenic hormone is necessary but not sufficient. Several authors have pointed out that crude anterior pituitary extracts will again initiate lactation in hypophysectomized mammals, whereas refined lactogenic extracts will not (Gomez and Turner, 1936; Nelson and Gaunt, 1936).

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It is probable that the successful initiation of lactation by means of the crude anterior pituitary extracts depends upon the presence of adrenal cortical stimulating hormone (as well as, perhaps, that affecting carbohydrate metabolism) in such extracts.[12] According to Gaunt and Tobin (1936), the adrenal glands contain no substance with lactogenic effects. However, after bilateral adrenalectomy has been performed in lactating rats, the secretion of milk ceases but can be restored by the administration of about twice the dose of adrenal cortical extract necessary to prevent death. Smaller doses can be used in conjunction with salt therapy, and sometimes salt therapy alone is sufficient. After hypophysectomy in lactating guinea pigs, lactation ceases but can be initiated again by the administration of refined lactogenic extract and adrenal cortical hormone (Gomez and Turner, 1936; Nelson and Gaunt, 1936.)[13] However, this treatment permits lactation for only a few days and does not prevent the involution of the breasts. Either extract by itself is of no value. Gomez and Turner (1937) later reported on the use of adrenal cortical stimulating hormone, obtained from the anterior pituitary, in place of adrenal cortical extract. By injecting an extract containing this hormone as well as lactogenic extract and glucose, they could maintain lactation in hypophysectomized guinea pigs for as long as 8–15 days.

The effects of "sex hormones" on lactation. 1. *Oestrogens.*— Numerous earlier reports indicated that the secretion of lactogenic hormone as indicated by lactation is inhibited by the internal secretions of the gonads. For example, ovariectomy may be followed promptly by lactation. On the other

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[12] Thyrotropic hormone may be of importance but certainly is not essential, inasmuch as lactation takes place in thyroidectomized mammals (see pp. 165–66).

Schooley, Riddle, and Bates (1937) found that the response of the crop-glands of one pigeon following the injection of lactogenic hormone was not prevented by adrenalectomy four days before.

[13] Gomez and Turner (1936–37) believed that it is important also to administer glucose, which they injected in amounts as high as 200 mg. per 100 gm. of body-weight daily.

hand, lactation may occur in spite of the continued injection of an oestrogen into mammals like the rat and rabbit.

A distinction should be made between the formation and storage of lactogenic hormone and its release in adequate amounts into the circulating blood. Recent experiments furnish us with some information on the effects of oestrogens on the storage of lactogenic hormone. Reece and Turner (1937) reported that the total amount (and often the concentration) of lactogenic hormone in the rat's anterior pituitary is increased following the injection of oestrone or oestradiol benzoate. The pituitary of the ovariectomized rat contained less lactogenic hormone in a lower concentration. Margulis (1936) concluded that the injection of "folliculin" into castrated rabbits is accompanied by an increase in the content of lactogenic hormone in the pituitary. However, Margulis used only a few animals.[14]

The inhibitory effect of oestrogens on lactation has been studied by other authors. Folley and White (1937) injected into male or female pigeons 5 mg. of oestradiol benzoate, followed a few days later by a dose of lactogenic hormone sufficient to cause a marked hypertrophy of the crop-glands. In birds also receiving oestradiol benzoate the hypertrophy of the crop-glands was only about one-half (males) to three-fourths (females) that in control birds. The injection of large doses of oestrogens may inhibit normal lactation in rats, guinea pigs, and rabbits (Folley and Kon, 1938; Mugnai, 1937; Smith and Smith, 1933; Custo, 1937). Folley and Kon ob-

[14] In Wiegand's experiments (1937) ovarian secretion was stimulated in rats, initially immature, by the injection of 100 rat-units of prolan daily for 15–20 days. The amount of lactogenic hormone in the pituitary was much greater than in control animals receiving no prolan. If, however, the injections were stopped and the ovaries were removed, lactation appeared after about 36 hours. At that time there had occurred a marked fall in the lactogenic action of the pituitary in agreement with the view that stored hormone had been discharged. Such an effect of gonadectomy was not observed in normal rats.

In other reports (1937) Wiegand attributed the marked increase in the amount of lactogenic hormone in the pituitary immediately following delivery to an increased formation of the hormone caused by the loss of the inhibitory effect of oestrone believed to be present during pregnancy in the rat.

served a definite but much less marked inhibition, if the ovaries were removed immediately following parturition in rats. Nelson (1937) observed lactation in guinea pigs (normal or gonadectomized of both sexes), when the injection of oestrone, which had caused a complete development of the breasts, was stopped. Also he reported that lactation after oestrone continued in hypophysectomized guinea pigs, if crude pituitary extract was injected; if injections of oestrone were again administered, the lactogenic action of the crude pituitary extract was inhibited. According to Richter (1936), spaying is not followed by any improvement in the quantity or fat-content of the milk in lactating cows; also the duration of lactation is not affected. However, the injection of an oestrogen like oestradiol benzoate is followed by a reduction in the quantity of milk produced by cows (Folley, 1936; Waterman, Freud, and Vos–De Jongh, 1936). Folley studied the effects of oestrogen on some of the constituents of milk and serum. The percentage of fat and non-fatty solids of milk was increased, whereas the nitrogen-partition was not affected, indicating that the milk was not colostrum-like. In the serum the treatment appeared to cause some increase in the concentration of inorganic P and, transiently, of phosphatase; also there was observed a temporary fall in the concentration of Ca.

Other investigators have studied the practical importance of oestrogens as means of suppressing lactation after abortion or stillbirth (Snoeck, 1935; Hoffmann, Mayor, van Tongeren, 1936; Mugnai, 1937). Such treatment is of value only when enormous doses are injected. Snoeck injected 100,000 international units of oestrone (?) within three days. Mayor as well as Mugnai concluded that the injection of 250,000 units (mouse-units [Mayor], international units [Mugnai]) of oestradiol benzoate can completely suppress lactation following delivery. Breast tension may be lessened by smaller doses. Mugnai recommended the use of oestrogen to inhibit

the discharge from fistulas of the breast following incision for abscess.

2. *Progesterone.*—Folley and Kon (1937–38) particularly doubt that the inhibition of lactation during pregnancy is caused by the secretion of progesterone. However, they admit that the inhibiting effect of oestrogen on lactation may be reinforced by progesterone, which by itself is without such action. In their experiments with lactating rats, they injected 1 mg. of progesterone daily to the mothers from the fifth day after parturition. There was no detectable effect on the weight-curve of the nursing young. Anselmino, Herold, Hoffmann, and Pencharz (1936) also used rats but concluded that progesterone can cause marked inhibition of lactation. The authors injected 200 rat-units of prolan daily for 14–18 days to bring about breast development in immature rats. The animals were then spayed, following which (36–48 hours) lactation appeared. Almost complete inhibition of lactation then followed the injection of two doses of 0.5 unit each of progesterone, whereas the administration of 4,000 units of oestrogen was without effect.[15]

3. *Androgens.*—Suitable doses of testosterone propionate apparently can completely inhibit lactation in intact lactating mice or rats, whereas androsterone has practically no effect (Robson, 1937; Folley and Kon, 1938). Robson injected 0.1 mg. of testosterone propionate in oil daily to lactating mice; nearly all the young died in less than three weeks. Similar injections of 0.2 to 0.4 mg. of androsterone were without action. Lactation (but not suckling or maternal care) rapidly disappeared, if 0.05 mg. of testosterone propionate suspended in 0.05 cc. of 10 per cent alcohol were injected every 2 hours. Control experiments indicated that the solvent did not contribute to the effect. The observations

[15] Folley and Kon (1938) found that the inhibitory action of oestrogen on lactation is less readily observed in spayed animals. The possible luteinization of the ovaries owing to the liberation of luteinizing hormone from the pituitary following the injection of a large dose of an oestrogen seems to have been left out of consideration.

of Folley and Kon were made in lactating rats. Lactation was markedly inhibited by the injection of 0.4 mg. of testosterone propionate per 100 gm. body-weight; on the other hand, three-fourths of this dose of androsterone had no effect. The authors suggest the generalization that substances which cause growth and development of the breasts also inhibit lactation.

OTHER BIOLOGICAL INTERRELATIONSHIPS OF THE LACTOGENIC HORMONE

New observations on the distribution of the hormone.—The concentration of lactogenic hormone in the pars glandularis of the sperm whale is less than 1.5 per cent of that in the anterior pituitary of the ox (Geiling, 1935). Leblond and Noble (1937) attempted to determine the amount of lactogenic hormone in the pituitary of animals of several classes. Their assays were performed in pigeons, into which they made injections intradermally over a crop-gland. They doubted the specificity of some responses because, although undulated thickenings were produced, the cells of the crop-gland contained few or no fat-granules (Scharlach R). The clearest responses were obtained by the injection of the pituitary of mammals (mice, rats, rabbits) or of birds (fowls, pigeons). Glands from various fishes were implanted, sometimes as many as 100 in a single assay. Attempts also were made to detect and determine the amount of hormone in the pituitary of an amphibian (*Rana pipiens*) and a reptile (*Kinosternon odoratum*).

The secretion of milk in response to the injection of extract containing the lactogenic hormone.—Grant (1936–37) has investigated the action of lactogenic extract on the regressing mammary glands of the guinea pig. Large doses of the hormone caused the transient reappearance of a small amount of mammary secretion which, however, contained little or no lactose (0.04–0.24 per cent). The volume of secretion was increased tremendously if preliminary treatment with oestra-

diol (0.5 mg. daily for 7 days) followed by progesterone (0.4 mg. daily for 4 days) was given.[16] De Fremery (1936) concluded that lactogenic extract can initiate the secretion of milk in the goat, irrespective of the season or the phase of the oestrous cycle. Other studies in lactating cows have been made by Waterman, Freud, and Vos–De Jongh (1936) and by Asimov and Krouze (1937). Only two cows were used by Waterman and others whose experiments indicated that lactation is favorably influenced by the hormone. Asimov and Krouze concluded that milk production is increased approximately 20–40 per cent by the injection of a crude anterior pituitary extract every 10 days. Five hundred and ten lactating cows which received injections were compared with 90 control animals. The effect of the extract was much greater in the first half of the normal period of lactation. Except for a temporary rise of 0.1–0.8 per cent in the concentration of fat, the milk was found to resemble normal milk. (The pH and the concentration of lactose and chloride were also studied.)

Among observations in primates are those of Geschickter and Lewis (1936), who studied the action of lactogenic extract in women who had received injections of oestrin for a month previously. The administration of a total dose of 600–1,120 bird-units of lactogenic hormone during a week was followed by the elaboration of a secretion which persisted only a few days, despite further injections or mechanical stimulation. Histological examination of breast tissue indicated that true lactation had not appeared. The authors believed that such combined treatment might cause changes resembling cystic disease of the breast.

The thyroid gland in relation to lactation.[17]—Lactation and,

[16] The injection of 80 units of pregnant-mare serum daily for 3 days prior to the injection of lactogenic extract appeared not to be of value.

[17] Riddle and others (1936–37) pointed out that lactogenic extracts may have a marked calorigenic action in pigeons. This effect, like similar effects of thyroid extract or thyrotropic hormone, can be observed at 30° C. At 20° C. the change may be slight, and at 15° C. it may be in the opposite direction. The calorigenic

therefore, the action of the lactogenic hormone do not depend on the normal secretion of thyroid hormone to any important extent. Schooley, Riddle, and Bates (1937) were able to produce a typical crop-gland response to lactogenic hormone in a thyroidectomized pigeon. In mammals like the dog, guinea pig, and rat, lactation following parturition or the withdrawal of oestrin or the injection of anterior pituitary extract is not prevented by thyroidectomy (Houssay, 1935; Nelson and Tobin, 1937). Likewise the development of the breasts during pregnancy is not significantly inhibited by thyroidectomy in the rat (Nelson and Tobin, 1937). Unlike adrenal cortical extract, thyroid extract or thyroxine administered coincidently with lactogenic extract will not initiate lactation in suitable hypophysectomized animals (Gomez and Turner, 1937; Nelson and Tobin, 1937).

De Fremery (1936) reported that doses of thyroxine sufficient to cause a severe hyperthyroidism (15 mg. daily) in goats brought about a reduction in the volume of milk secreted daily. No change in the composition of the milk was noted. After the administration of thyroxine was stopped, the output was not restored to its original level. Van Tongeren (1936) could demonstrate no action of thyroxine in lactating women. Probably the doses he used were too small.

Miscellaneous observations.—Additional evidence in favor of the view that broody behavior of fowls depends upon the lactogenic hormone has been gathered by Burrows and Byerly (1936). The authors compared the proliferative changes in the crop-glands of pigeons by implanting one pituitary (e.g., from a broody hen) over one crop-gland and the other (e.g., from a laying hen) over the other crop-gland.

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action of lactogenic extract is not prevented by thyroidectomy. Riddle, Dotti, and Smith suggest that a moderate increase (about 20 per cent) in the blood-sugar concentration as well as a calorigenic effect are caused by an action of lactogenic hormone on adrenal cortical tissue.

The concentration of sugar in the blood of the normal rabbit or of the normal or depancreatized monkey is not affected by the injection of lactogenic extract (Nelson, Turner, and Overholser, 1935).

The pituitary gland of broody hens produced much more hypertrophy of the crop-gland than that of laying hens or of cocks. Other comparisons between the pituitaries of hens of broody or non-broody genetic constitution indicated again that broodiness is associated with the larger amount of lactogenic hormone in the pituitary.

Leblond and Nelson (1937) concluded that the maternal instinct in lactating mice and rats does not depend upon the secretion of lactogenic hormone because the instinct persists after hypophysectomy.

De Fremery (1936) was able to terminate pregnancy, either as fetal death or abortion, by the injection of lactogenic extract into pregnant goats, guinea pigs, rabbits, or rats. He stated that the effect was not due to gonadotropic or thyrotropic hormone.

According to Salle and Schechmeister (1936), embryonic crop-gland cultured *in vitro* is not affected by lactogenic extract. The growth of the Simpson mammary carcinoma in mice is not altered after the injection of 60 bird-units of lactogenic hormone (Bischoff and Maxwell, 1936).

The metabolism of the lactogenic hormone.—Wiegand (1937) found that little change in the amount of lactogenic hormone is found in the pituitary body of the rat during pregnancy. Immediately after parturition the amount present is doubled or trebled; however, the quantity of the stored hormone falls as it is liberated into the blood stream and lactation appears. Perhaps a similar change occurs in women. At any rate, several authors have demonstrated lactogenic hormone in the urine of lactating women. Like Wiegand, these authors relied on the hypertrophy of the pigeon's crop-gland to detect the hormone.[18] Lactation in new-born children—the secretion of "witches' milk"—is attributed by Lyons (1937) to the action

[18] Lyons and Page (1935), Hoffmann (1936), and Tesauro (1936). Lyons and Page estimated that the daily excretion of hormone in the urine of women 4–13 days after parturition was at least equivalent to what can be extracted from one pars glandularis of the ox. Liard's experiments (1937) appear not to be adequately controlled.

first of oestrin and then of lactogenic hormone. He was able to detect lactogenic hormone (0.03–0.5 unit[19] per cc.) in the urine of new-born babies. Two units[19] per cc. of urine were excreted by a lactating baby boy.

Reece and his associates investigated the concentration and total amount of lactogenic hormone, as assayed in pigeons, in the pituitary of rats with various vitamin deficiencies. There appeared to be a reduction in the total amount of hormone, if the diet was deficient in vitamins A, B (as B complex), and D; however, the concentration of the hormone was increased in vitamin-B deficiency, whereas if vitamin A, or especially vitamin D, was lacking, the concentration was diminished. No change in the total amount or concentration of the hormone accompanies vitamin-E deficiency.[20]

According to Lewis and Geschickter (1936), cyst fluid of cystic disease of the breast, although sometimes without action, contains on the average about 500 bird-units of lactogenic hormone per liter. Colostrum as well as the tissue of the udders of lactating cows contain lactogenic hormone (Geschickter and Lewis, 1936).

The lactogenic extract used by Giuffrida (1937) was administered repeatedly to pigeons. The maximum hypertrophy of the crop-glands was observed after seven daily injections. The effects disappeared despite injections for a longer period. Refractoriness toward the extract appeared earlier if larger doses were used. Young (1937) prepared an extract with lactogenic and diabetogenic effects but without significant action on either the thyroid or the gonads. Although this extract was injected daily—in some instances for as long as 9 weeks—into rabbits, dogs, or monkeys, the sera of these animals not only contained no lactogenic "an-

[19] Intradermal "micro-units" in the pigeon.

[20] Marchesi (1935) administered gonadotropic extract, so that pregnancy and parturition took place in animals presumably receiving no vitamin E. Lactation either did not appear or was hopelessly inadequate.

tihormone" but even seemed to augment the action of the hormone.

The assay of lactogenic hormone.—The only satisfactory methods of assaying the lactogenic hormone are based upon the response of the crop-glands of pigeons—a test introduced by Riddle and his colleagues. After the injection of extract containing lactogenic hormone, the crop-glands undergo hypertrophy which may be limited to only one of the two glands, provided that not too large a dose is injected into the skin overlying the gland. Pigeons of the same stock vary greatly, of course, in sensitivity. Some varieties of pigeons are more suitable than others; Bates and Riddle (1935) found that a tenfold variation in sensitivity may be encountered in different races of pigeons (see also Evans, 1937). Wolff (1937) concluded that the response of young birds is more regular than that of adults. Birds of either sex can be used.

The effect of a dose of lactogenic hormone depends upon the route of absorption. The greatest response follows the intracutaneous administration of extract over a crop-gland. The dose causing a given response is about 1 per cent of that necessary, if injection is subcutaneous, intramuscular, or intraperitoneal (Lyons and Page, 1935; Bates and Riddle, 1936; and Chasin, 1936). According to Bates and Riddle (1936), the relative efficacy of injected hormone is approximately the following: intracutaneous, 1,000; subcutaneous, 10; intramuscular, 2; intraperitoneal, 1.3; and intravenous, 0.9.

Varous authors[21] have devised methods of assay and have often determined the relationship between dose and response, which usually is given in terms of crop-gland weight, sometimes in relation to body-weight. Potency also may be estimated from the percentage of birds in which a minimum response is produced. Probably few investigators will oppose the view that a standard preparation, perhaps crystalline

[21] Bates, Riddle, and Lahr (1936), Dyer (1936), McShan and Turner (1936), Lyons (1937), Rowlands (1937).

hormone, must be introduced. An example of the relationship between dose and response is the graph of Rowlands reproduced in Figure 21. Rowlands' extract, which contained neither gonadotropic nor thyrotropic hormones, was injected subcutaneously once daily for 6 days when the maximum effect was observed. The crop-glands were removed on the seventh day, fixed in Bouin's fluid, and weighed after they had been carried to 70 per cent alcohol. Weights of
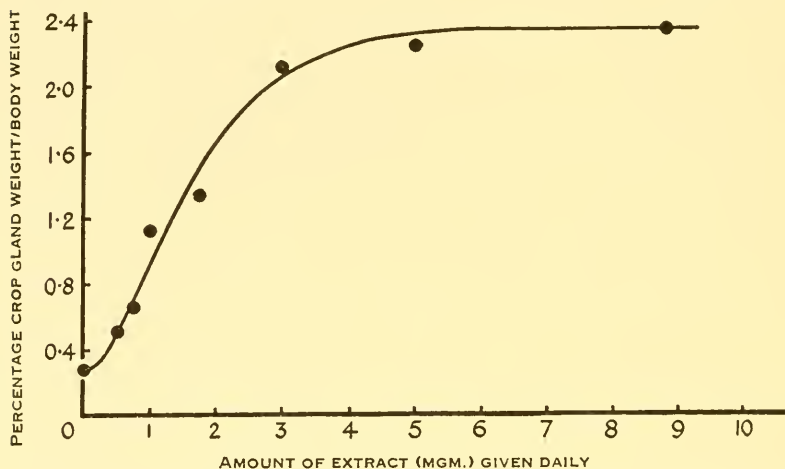
Fig. 21.—The relationship between the dose of anterior pituitary extract (containing lactogenic hormone) and the growth of the crop-gland of the pigeon. (From Rowlands, Quart. J. Pharm. Pharmacol., 10, 216–21 [1937].)

crop-glands are expressed as percentages of body-weight. In birds receiving no injections the crop-glands constitute about 0.3 per cent of the body-weight. Rowlands recommended that the glands of injected birds should fall within a weight-range represented by 0.8–2.0 per cent of the body-weight.

Leblond and Allen (1937) stated that the action of lactogenic hormone could be detected as soon as 10 hours after injection, if 0.5 mg. of colchicine also was administered. After the injection of either the hormone or colchicine, about 2 per cent of the cells of the crop-glands were in mitosis; however, if both were injected, "arrested" mitoses were present

in about 20 per cent of the cells. According to Valle (1937), smears of the cells of crop-gland secretion can be obtained by means of a fistula. Especially 48–72 hours after the injection of lactogenic extract, the cells are found to contain orange-colored droplets of various sizes after fixation in formalin and staining by sudan III and methylene blue.[22]

The chemistry of the lactogenic hormone.—White, Catchpole, and Long (1937) recently described a method of isolating a crystalline lactogenic principle which presumably is the pure hormone. By the two-day intracutaneous test of Lyons and Page a "unit" was found to be 0.05–0.1 γ; by a systemic test, also in pigeons, 0.1 mg. was designated a unit. The method used was briefly as follows: 100 mg. of purified extract was dissolved in 2 cc. of 13 per cent acetic acid to which was added 2 cc. of 13 per cent pyridine. The cloudy mixture was set aside and later centrifugated. The precipitate was subjected to the same treatment—the whole process being repeated ten times. Crystalline hormone was finally obtained either by allowing the acetic acid-pyridine mixture to stand in the refrigerator or by the careful addition of 1 per cent NH_4OH to the mixture followed by centrifugation and refrigeration of the turbid mother-liquor. The crystalline material yielded on analysis 51.11 per cent of C, 6.76 per cent of H, 14.38 per cent of N, and 1.77 per cent of S. It appeared to be protein or protein-like. The following reactions were positive: xanthoproteic, biuret, labile S, Millon, and Hopkins-Cole.

Other reports are of interest so far as the preliminary purification of the hormone is concerned.[23] The most varied media have been used for initial extraction: 60–70 per cent alcohol at "pH" 9–10 (this was used by Bates and Riddle

[22] Leblond and Nelson (1937) and Leblond and Noble (1937), who injected material intracutaneously, concluded that non-specific proliferation of the crop-glands can be produced (e.g., by liver). In proliferation not due to lactogenic hormone, fat-granules are not found in the growing epithelium.

[23] Bates and Riddle (1935), Bergman and Turner (1937), Evans (1937), Lyons (1937), and McShan and French (1937).

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and is recommended by Bergman and Turner), dilute acetic acid or acidified acetone (Lyons, and McShan and French), 0.05 N NaOH (Evans). The further details of preparation can be found in the reports of the various authors.

McShan and French confirmed the statement of Bates and Riddle that purified extracts withstand boiling in a solution of pH 8. If the substance is a protein, this is a remarkable property. So far, this experiment has not been performed with crystalline hormone. In a solution at a lower or a higher pH, the hormone is inactivated at a temperature of 100° C.

SUMMARY

The manner in which the anterior pituitary controls the development of the breasts and the secretion of milk is more complex than was suspected a few years ago. The important and probably essential glands of internal secretion are the pars glandularis of the pituitary body, the ovaries,[24] and the cortex of the adrenal glands.

For the growth and development of the breasts, an oestrogen analogous to what is obtained from ovarian tissue must be secreted or injected. In some mammals like the guinea pig this appears to be the only ovarian secretion required for prelactation development. In other mammals like the rabbit it is believed that corpus luteum hormone (progesterone) is also required later. However, development of the breasts due to an oestrogen is prevented by hypophysectomy. Also, there is other evidence that an anterior pituitary secretion, which brings about development of the mammary glands, is formed and liberated into the blood stream in response to ovarian (or placental) secretion or to the injection of an oestrogen. A working hypothesis regarding the growth and development of the breasts is as follows: gonadotropic hormones from the anterior pituitary are essential for the

[24] For the purposes of this summary, breast development and lactation in male animals will not be specifically considered. It may be mentioned that the development of the rudimentary breasts of male animals appears to depend upon the testes and the anterior pituitary.

normal secretory activity of the ovaries; ovarian secretions (or placental secretions, or both in pregnant animals) bring about the elaboration of a new anterior pituitary secretion which causes growth and development of the mammary glands.

Provided that prelactation development has occurred in the breasts, another anterior pituitary hormone—the lactogenic hormone—brings about lactation. However, this hormone alone cannot initiate lactation in hypophysectomized animals. Perhaps because of its effects on salt metabolism, adrenal cortical hormone must also be available to the organism. In hypophysectomized animals lactation from adequately developed breasts can be initiated by the injection of lactogenic hormone in combination with adrenal cortical hormone from the adrenals or adrenal cortical stimulating hormone from the pituitary. It is probable that the maintenance of lactation depends upon additional hormones, including those responsible for the continued development of the breasts.

The greater part of the attention of investigators has been focused on the lactogenic hormone. This substance apparently has been isolated as a crystalline substance, which is either a protein or is closely related to proteins. It is conveniently assayed by its stimulating effect on the growth of the crop-glands in the pigeon. In the rat, at least, its liberation from the pars glandularis largely depends upon centripetal nervous impulses due to suckling. The amount of hormone secreted during lactation may exceed the needs of the mammary glands, so that the unused portion is excreted in the urine. Other data concerning the physiology of the lactogenic hormone are discussed not only in this chapter but also in the two which precede it.

CHAPTER VI

THE THYROTROPIC HORMONE

ONE of the impressive effects of hypophysectomy in mammals is a marked fall in the rate at which heat is produced. This change is due principally to inadequate function of the thyroid gland and can be correlated with morphological changes in the thyroid—i.e., undischarged colloid accumulates in vesicles lined by flat, "inactive," epithelial cells. A specific substance called the thyrotropic hormone is secreted only by the anterior pituitary;[1] it is responsible for the maintenance of normal thyroid function and may be important in disorders attributed to deficient or excessive thyroid secretion. In classes of animals other than mammals different changes, likewise dependent on the virtual absence of thyroid secretion, follow the removal of the pars glandularis. A well-known example is the absence of metamorphosis after the removal of the gland from anuran larvae.

The thyrotropic hormone has not been isolated as a pure substance. Nearly all the recent progress is concerned with its biological action.

The biology of thyrotropic hormone in fishes, amphibia, and reptiles.—Young and Bellerby (1935) were not successful in attempts to produce metamorphosis in lampreys (*Lampetra planeri*) by the injection of an extract of the anterior pituitary of the ox.

The pioneer work of Adler, Smith, and Allen clearly demonstrated that metamorphosis in anuran amphibia is pre-

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[1] Sturm and Schöning (1935) believed that extracts of the ovary or the medulla of the adrenal gland may act like true thyrotropic hormone. Repetition of their work with ovarian tissue yielded no confirmation (Ballif and Gherscovici, 1936; McGinty and McCullough, 1936; and Emerson, 1937).

vented by the removal of the anterior lobe or the buccal anlage of the pituitary, because what is now termed thyrotropic hormone is no longer available. Without thyrotropic hormone from the anterior pituitary, thyroid function is so deficient that metamorphosis is prevented. The experiments of Voitkevič (1937), who used larvae of *Rana esculenta* and *R. temporaria*, confirm observations—i.e., such as the greater thyrotropic effect of implants of basophilic chromophils in comparison with oxyphilic chromophils—which have already been discussed in my monograph of 1936. The author's observation that implants of beef anterior pituitary containing oxyphils as the principal chromophil antagonize spontaneous metamorphosis or metamorphosis caused by anterior pituitary basophils or thyroid extract has not been independently confirmed. Etkin's study (1935), in which larvae of *R. sylvatica* were used, led to the following conclusions: (1) The pars buccalis is self-differentiating (i.e., differentation occurs after its transplantation to a new site), (2) thyrotropic hormone is secreted in an amount proportional to the amount of actively secreting pituitary tissue, and (3) the liberation of the hormone appears not to depend on nerves. Metamorphosis occurred at about the normal age and stage of growth in embryos which had been hypophysectomized and given replacement therapy in the form of a transplant of the removed pituitary which was placed in the eyecup or under the adhesive disk. If similar embryos received three transplants of the pars buccalis under the adhesive disks after hypophysectomy, precocious metamorphosis (at 8 instead of the normal 18 days) followed; also, the length of the larvae was less than that of normal larvae at the time of the corresponding change (29 instead of 44 mm.). According to Atwell (1935), the differentiation and subsequent secretory activity of the anterior pituitary in larvae of *R. sylvatica* or *R. pipiens* can take place without contact with nervous tissue or foregut. (Atwell could not be sure that this statement holds for the pars intermedia; also, he stated that Etkin's

transplants were not free from nervous tissue.) Similar experiments in *Amblystoma punctatum* were unsuccessful.[2]

Atwell (1937) found that compensatory hypertrophy of thyroid fragments in larvae of *R. pipiens* is prevented by hypophysectomy. This finding is in accord with other work in amphibia and mammals.

Another group of authors has published observations largely confirming and extending previously reported experiments in urodele amphibia. Uhlenhuth and his collaborators[3] again described the stimulating effect of anterior pituitary extract on the thyroid as indicated by morphological changes in the latter, by increased oxygen-consumption or by precocious metamorphosis. Most of their observations were made in *Amblystoma tigrinum*. The photomicrographs of Figure 22 are reproduced from those published by Adams and Martindale (1936). The injection of an alkaline extract of the pars glandularis of the ox ("Phyone") produced a marked stimulation of thyroid function in hypophysectomized newts (*Triturus viridescens*). Maximum changes were produced after daily injections had been given for about three weeks. The thyroid underwent regression to its former condition, characteristic of hypophysectomy, only weeks after injections were stopped.

Hypophysectomy prevents molting in adult urodele amphibia and, in this respect, resembles thyroidectomy. The cornified cells of the epidermis are retained as successive layers. These effects of extirpation of the pituitary do not occur in larval urodeles or in neotenous forms, except perhaps in *Necturus maculosus* (Osborn, 1936). Adams and Gray (1936) were able to cause molting of the layers of cornified epidermis of hypophysectomized newts (*T. viridescens*) by the administration of anterior pituitary extract, thyroxine, or

[2] Blount's results in *Amblystoma* indicated that the pars neuralis is required for the differentiation of the pars glandularis. In his animals there also were a pronounced intensification of pigmentation and distortions of growth.

[3] Uhlenhuth and Schwartzbach (1935); Uhlenhuth, Schwartzbach, and Thompson (1935); and Schwartzbach and Uhlenhuth (1936).
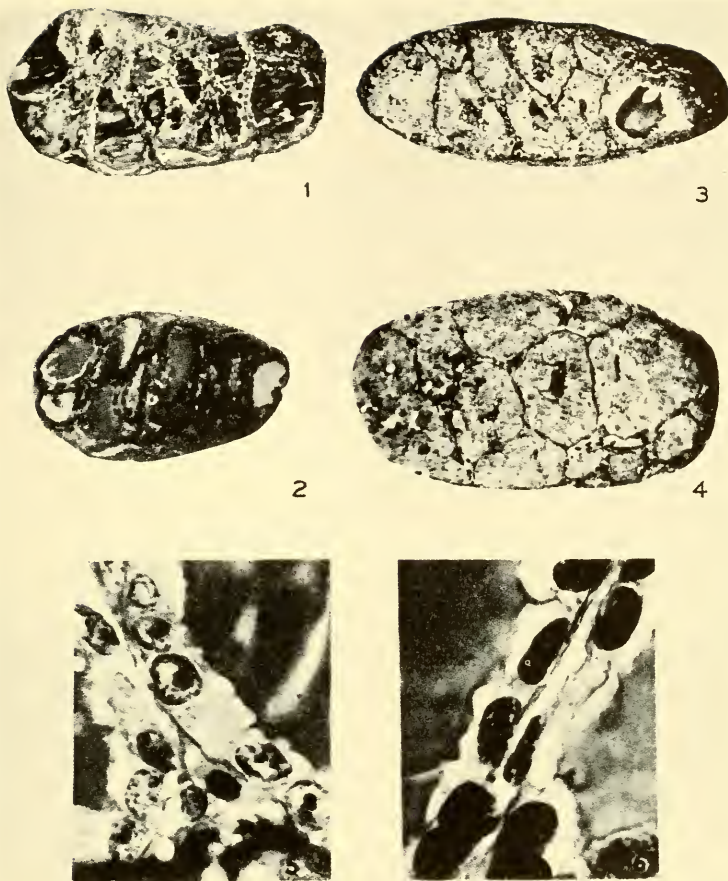
FIG. 22.—The effects of hypophysectomy and of the injection of anterior pituitary extract after hypophysectomy on the thyroid gland of the newt, *Triturus viridescens*. (From Adams and Martindale, Anat. Rec., **65**, 319–31 [1936].)

1, 5, Photomicrographs of thyroid of normal newt at low and high magnifications. *2, 6,* Photomicrographs of thyroid of newt 5 weeks after hypophysectomy. *3,* Photomicrograph of thyroid of newt receiving anterior pituitary extract for 10 days. Treatment was begun 5 weeks after hypophysectomy. *4,* Treatment begun as in *3,* but continued for 20 days. Photomicrographs *1–4* were made at the same low magnification, photomicrographs *5–6* at the same high magnification.

iodine, or by grafts of the thyroid. Anterior pituitary extract was effective because it contained thyrotropic hormone. The mechanism by which iodine facilitates molting in such animals is not clear; the element produced no morphological change in the thyroid gland.

After hypophysectomy, repeated molting occurs in snakes (*Thamnophis sirtalis, T. radix*) (Schaefer)—the reverse of the effect induced in urodele amphibia. Hellbaum (1936) recently described the effects of hypophysectomy as well as those following the injection of anterior pituitary extract into such snakes. The cytological changes in the anterior pituitary of thyroidectomized snakes (*T. radix*) were investigated by Siler (1936).

Recent observations in birds.—After the complete removal of the pituitary from Brown Leghorn cocks, the feathers finally resemble those of thyroidectomized cocks—loss of black pigment of feathers of part of the neck, of the breast, and of the legs. Hill and Parkes (1935), who made this observation, were able to restore the pigment to normal by administering thyroxine to a hypophysectomized cock.

The biology of the thyrotropic hormone in mammals.— Numerous experimental observations with a great variety of objectives have been made in mammals. Much of the work only adds adornment to knowledge previously available; in addition, however, new facts have been gathered. The classification of extensions of our knowledge as well as additions to it will now be attempted.

The effects of thyroidectomy on the anterior pituitary.—Hypertrophy of the pars glandularis, which is often more marked in male than in female animals, usually follows thyroidectomy. It is generally agreed that an important histological change in the anterior pituitary is a marked reduction in the proportion of oxyphils. Also there is an increase in the percentage of cells with an affinity for basic dyes; such cells, often first undergoing hypertrophy, may become vacuolated or appear to be filled with hyaline material and usually are

identified as "thyroidectomy-cells." Their origin is still a matter of disagreement. Some authors believe that they arise at least partly from basophils and either are identical with "castration-cells" or are completely different.[4] Their relationship to the hypertrophied reserve cells which other authors have so frequently noted in the anterior pituitary of animals with thyroid deficiency probably also is close.[5]

Lebedewa (1936) believed that the pituitary of young thyroidectomized rats contains less thyrotropic hormone than normal. However, her conclusion is not based on enough experiments to warrant its acceptance. According to Zeckwer (1936), although the concentration of thyrotropic hormone in the pituitary of thyroidectomized rats is greater than normal in terms of body-weight, the amount present is less than normal in terms of age.[6] Chen and van Dyke (1936) investigated the anterior pituitary of normal and thyroidectomized rabbits. In littermate normal animals there was no sexual difference in thyrotropic potency. Three months or more after thyroidectomy an increase in the total amount of hormone in the hypertrophied anterior pituitary of female rabbits was noted. Although hypertrophy of the gland was greater in male rabbits, a similar change in potency could not be found. In both sexes the hypertrophied anterior pituitary associated with thyroid deficiency contained more water than the normal gland (total solids 19.1–19.4 per cent compared with the normal of 22.2–23.7 per cent).

The effects of hypophysectomy on thyroid function.—There is little to add to the previous account. Normal thyroid function and all that this implies is markedly but not completely deficient after hypophysectomy. Low-grade thyroid

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[4] See chap. i, p. 22.

[5] Altschule and Cooper (1937) recently reported on the changes in the human pituitary associated with operative or spontaneous hypothyroidism. They concluded that the number of basophils, often markedly vacuolated, may be 2–4 times as great as normal. Like other authors they believed that hypothyroidism may be due to a primary disturbance of either the pars glandularis or the thyroid.

[6] See also Zeckwer and others (1935).

activity is indicated morphologically by the atrophy of the epithelium of the thyroid follicles and the distention of the latter with dense, non-vacuolated colloid. Such changes were again reported by Rowlands (1935), who hypophysectomized fowls and mammals of several species (ferret, guinea pig, and hedgehog). It is of interest that weight-atrophy does not follow hypophysectomy in the guinea pig. The morphological signs of inactivity of the thyroid could be observed in the various animals 1–2 weeks after hypophysectomy.[7]

Other aspects of the biology of thyrotropic hormone.—The most significant action of thyrotropic hormone is to facilitate or promote the discharge of thyroid hormone from the thyroid gland. The colloid becomes vacuolated; the thyroid vesicles diminish in size; the epithelial cells become hypertrophied. Its further effect is to promote hyperplasia of the epithelium, so that doses much larger than those causing the discharge of stored hormone may bring about marked hypertrophy of the thyroid. There still is disagreement as to the unity or duality of the anterior pituitary hormone(s) causing these two principal effects.

Several new reports concerning the amount of hormone in the pituitary body of various mammals have been published. Müller, Eitel, and Loeser (1935) declared that the human gland contains 5–30 "guinea pig units." Undoubtedly there was great variation in the degree of postmortem autolysis in their material. The variations in potency were great and appeared not be be related to age or sex; high values were obtained if death was due to tuberculosis or other infections. According to Saxton and Loeb (1937), the amount of thyrotropic hormone in the human pars glandularis is quite constant irrespective of age or other factors such as pregnancy and lactation. Rowlands (1936) used a reliable uni-

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[7] Reiss and Fischer-Popper (1936) injected 0.1–0.5 mg. of thyroxine daily into rats. They concluded that after hypophysectomy the sensitivity of such animals was greatly increased (loss of body-weight, increased rate of urinary excretion of N, increased basal metabolic rate), because compensating "antithyroid" effects of the pituitary, mediated through the adrenal glands, were absent.

form method of assay (hypertrophy of the guinea pig thyroid according to Rowlands and Parkes). Two methods of initial extraction of the same acetone–desiccated powders were employed with the results shown in Table 5. From this data it appears that the best practical sources of thyrotropic hormone are the pituitaries of cattle and pigs.[8]

TABLE 5

POWDERED PITUITARY OF	UNITS PER GRAM OF DESICCATED POWDER AFTER INITIAL EXTRACTION WITH	
	N/10 NaOH	50 Per Cent Pyridine
Dog.....................	43	....
Horse.................	5[*]	....
Ox.....................	20	28
Pig....................	40	54
Sheep.................	8	16

* Anterior lobe only. Apparently the other figures refer to whole pituitary.

The effects of the injection of pituitary extracts containing thyrotropic hormone. 1. *Morphological changes in the thyroid gland.*—The response of the thyroid of different animals to thyrotropic hormone probably varies widely. A good example is the great susceptibility of the guinea pig's gland in comparison with the insensitivity of the rat's thyroid. With doses near the threshold, all parts of the gland are not equally sensitive; in the thyroid of the guinea pig the first and more pronounced changes due to thyrotropic hormone are observed in the central part of the thyroid lobes. Compensatory hypertrophy of the thyroid following partial extirpation depends upon the secretion of thyrotropic hormone by the anterior pituitary. Albani's recent report (1936) indicated that in young dogs this may be a very slow process, different from

[8] The anterior pituitary of the ox contains a higher concentration of thyrotropic hormone than that of the guinea pig (Emerson, 1937); however, the rat's gland contains 7–9 times as much as that of the ox (McQueen-Williams, 1935).

the rapid, dramatic changes which can be induced by anterior pituitary extract; however, this is hardly proof, as the author suggests, that the mechanisms involved are different. Extracts containing thyrotropic hormone probably facilitate the survival and growth of transplants as has again been reported by Eitel (1936). According to Koch, Schreiber, and Schreiber (1937), the peripheral growth of a transplant of the thyroid in the guinea pig is facilitated, if thyroid and pituitary tissue are transplanted together.

For some years it has been known that the rate of mitotic division of thyroid epithelium may be greatly increased in a mammal like the guinea pig, if anterior pituitary extract (thyrotropic hormone) be injected. An enormous change was reported by Kippen and Loeb (1935), who injected anterior pituitary extract into immature guinea pigs and removed the thyroid gland 48 hours later. In comparison with the normal thyroid in which was found an average of about 150 mitotic figures, the thyroid of injected animals contained as many as 190,000 mitotic figures. The effects observed by Bastenie and Zylberszac (1937) were clear cut but much less pronounced. These authors also injected colchicine (about 0.8 mg. per kg. body-weight) to bring out clearly the action of thyrotropic hormone on mitotic division.[9] Guinea pigs weighing 220–250 gm. were used. In thyroid tissue from control animals 6.3 mitotic figures per 100 follicles were found. The number increased to 16.8 after the injection of thyrotropic hormone. However, if both thyrotropic hormone and colchicine were injected, 119 mitotic figures—in the prophase for the most part—were found in 100 follicles.

Halpern (1935) investigated the action of anterior pituitary extract or KI on the appearance of the mitochondria and Golgi apparatus of epithelium of the thyroid of rats 2.5–3 months old.

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[9] Bastenie and Zylberszac mention two interpretations of the manner in which colchicine acts: it may bring about an increased rate of karyokinesis (Dustin) or it may arrest karyokinesis before the process is completed (Allen and others).

2. *Physiological, pharmacological, and biochemical aspects of the action of thyrotropic hormone.*—The administration of sufficiently large doses of anterior pituitary extract rich in thyrotropic hormone into a susceptible animal like the guinea pig may produce a "syndrome" strikingly resembling Graves's disease in man. These changes, of course, are prevented by thyroidectomy. Friedgood's article (1934) contains a discussion of the manner in which symptoms in guinea pigs may develop in relation to the administration of extract toward which refractoriness finally appears. The basal metabolic rate rises at first but later returns to normal, whence recrudescences of an elevated rate may appear. The rate is not necessarily high, although a well-pronounced thyroid hyperplasia may persist. Exophthalmos likewise is not necessarily associated with an increased rate of basal metabolism and may still be present after a long series of injections. Pathological changes in organs like the heart, kidneys, and liver are not like those of Graves's disease in man (Heinemann, 1937); however, this is not surprising. A number of authors have offered evidence indicating that an increased concentration of thyroid hormone is present in the blood after the gland has been stimulated by thyrotropic hormone. Zunz and La Barre (1935) found that the concentration of thyroid hormone in the serum of dogs is increased 2–4 times only 30 minutes after the injection of 60–80 guinea pig units of thyrotropic hormone. (Thyroid hormone was estimated by the method of von Euler and Holmquist.)

Several authors have paid particular attention to the indirect effect of thyrotropic hormone on the oxygen-consumption of man and animals under basal conditions after the administration of thyrotropic hormone.[10] Observations in man

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[10] According to O'Donovan and Collip (1937), pituitary extract may contain a substance causing an elevation of the basal metabolic rate persisting only a few hours after injection. The authors concluded that this substance is not thyrotropic hormone but probably is related to or identical with the melanosome-dispersing hormone of the pars intermedia and that it accelerates the rate of oxidation of fat.

Kuschinsky (1935) reported that if rats were kept at 4° C., their pituitaries con-

have been reported by Lederer (1935), Sylla (1935), Thompson and others (1936), and Scowen (1937). Thompson and his colleagues found that extracts containing thyrotropic hormone were without action, if thyroid tissue capable of function was lacking, as in certain patients with marked myxedema. The basal metabolic rate could be raised to normal (mild or moderate hypothyroidism) or elevated (non-toxic goiter), sometimes strikingly (exophthalmic goiter). Apparently because of the development of "antihormone," the change induced was only temporary and could not be elicited by a second course of injections. Sylla listed three therapeutic uses to which he put an extract containing thyrotropic hormone: (1) to cause complete recovery from pituitary cachexia, (2) to cause a loss of weight in obesity of certain types, and (3) to inhibit diuresis in a single patient with diabetes insipidus, as effectively as after the injection of extract of the posterior lobe. Lederer as well as Scowen has described the beneficial effects of the treatment of hypothyroidism due to pituitary insufficiency by the injection of extracts containing thyrotropic hormone. Measurements of the basal metabolic rate furnished objective proof of the favorable action of the hormone. Scowen found that much larger doses of thyrotropic hormone did not affect the basal metabolism of patients with classical myxedema, whereas the administration of thyroxine Na caused a prompt response. Presumably

tained about the same amount of thyrotropic hormone in association with histologic signs of diminished (at first) or increased (later) thyroid function. However, thyrotropic hormone might almost disappear from the pituitary of animals with inactive thyroids because of an environmental temperature of $38°$–$40°$ C.

See also the reference to the observation of Riddle and others (pp. 165–66). Riddle, Smith, and Moran (1935) found that the basal metabolic rate of pigeons is reduced as a result of hypophysectomy (-33 per cent at $30°$ C. or -17 per cent at $20°$ C.). If 10–23 per cent of the gland remained, there was a definite, but less pronounced, fall.

The hypophysectomized rat adapts itself slightly but very poorly to a cold environment (Wolf and Greep, 1937). Its body temperature is abnormally low (e.g., $34°$–$35°.5$ C. after 29 days in an environment at $2°$–$4°.5$ C.). In the thyroids of such animals is found some colloid absorption at the periphery; the central part of the gland is atrophic.

such patients suffer from a purely "thyrogenic" hypothyroidism.

Mahaux (1937) found that the elevation of the basal metabolic rate of guinea pigs, an effect ordinarily appearing about 48 hours after the injection of a large dose of thyrotropic hormone, was absent if 1 mg. of thyroxine had been administered. (The calorigenic action of thyroxine was allowed to decay before thyrotropic hormone was administered.) Likewise using guinea pigs, Gessler (1936) reported that oestradiol or its benzoate (5.0 mg.) caused a fall in the basal metabolic rate of 3–23 per cent. The oestrogen also appeared to lessen the calorigenic action of thyroid extract. Sherwood and Bowers (1936) stated that the injection of oestrone or oestrin may lower the basal metabolic rate of rats as much as 28–54 per cent. Also, the return of the rate to normal, after a marked elevation had been caused by thyroid extract, was accelerated by the injection of oestrin. Oestrogens appear to antagonize the action of thyroid hormone, not that of thyrotropic hormone as Gessler (1937) suggested. In the dog, according to Zajic (1935), the increased metabolic rate following the injection of thyrotropic hormone is not accompanied by any change in the respiratory quotient.[11]

Extracts containing thyrotropic hormone readily cause exophthalmos in thyroidectomized guinea pigs (Smelser, 1936; Paulson, 1937); therefore, this change cannot be caused by an increased secretion of thyroid hormone. Smelser even found that exophthalmos is more readily produced in thyroidectomized guinea pigs. He studied anatomically the contents of the orbit in normal animals and those with experimental exophthalmos. The increase in the bulk of the retrobulbar tissues amounted to as much as 40 per cent, because of hypertrophy of the fatty connective tissue, the dorsal lacrimal gland, the extraocular muscles, etc. As in certain instances of exophthalmos associated with a low basal metabolic rate in man, a fluid containing lipoid droplets and gran-

[11] See also O'Donovan (1937) and Sinha (1937).

ules as well as lymphocytes was found to infiltrate the orbital tissues. Paulson particularly described degenerative changes in the lacrimal glands sometimes associated with similar alterations in the extraocular muscles and, occasionally, in the orbicularis oculi. Altered activity of the sympathetic nervous system appears not to be a factor (Smelser).

Eitel's observations (1936) are in accord with other views that the action of thyrotropic hormone does not depend on peripheral nerves innervating the thyroid. On the other hand, Uhlenhuth (1937) believed that the effectiveness of thyrotropic hormone in salamanders or guinea pigs is increased if epinephrine or pilocarpine is also injected; however, he was not certain that this phenomenon was due to action on peripheral fibers of the autonomic nervous system. The experiments of Scharrer and Gaupp (1935) led them to conclude that thyrotropic hormone is not secreted by diencephalic "glands" (neurons of the supraoptic and paraventricular nuclei). As a result of hypophysectomy, toads do not molt. This defect is due to a deficiency of thyrotropic hormone and is not corrected by the administration of as many as three diencephalic "glands" rich in colloid.

One aspect of the possible interrelationship of the gonads and thyrotropic hormone has already been discussed in the section dealing with the action of thyrotropic hormone on the gaseous metabolism (p. 185). Certain other aspects of this interrelationship remain for consideration.[12] Voss (1935) was able to produce oviposition in the axolotl as many as three times a year by the injection each time of 120 guinea pig units of thyrotropic extract.[13] In confirmation of Riddle and Krizenecky, Mârza and Blinov (1936) found that the thyroid of the pigeon appears histologically to be more active at times of sexual activity and ovulation. According to Chouke, Friedman, and Loeb (1935), mitotic activity in the guinea

[12] See chap. iii, pp. 94–95.

[13] Adams and Hilsman had shown that pituitary transplants cause oviposition.

pig's thyroid is highest during the ovarian luteal stage and lowest during the follicular stage. Female thyroids appeared to be more active than those of male animals. Likewise, Franck (1937) declared that the injection of oestrone (250–2,500 international units) into guinea pigs is followed by histological signs of thyroid inactivity. The young male albino rat was the experimental animal chosen by Amilibia, Mendizábal, and Botella-Llusiá (1936). They believed that the daily injection of 200 mouse-units of oestrin ("Progynon") for 5 days causes the histologic changes commonly described as characteristic of increased thyroid activity and that this is due to an effect on the anterior pituitary. Also, they stated that a stage of thyroid inactivity followed that of activity.[14] According to Cramer and Horning (1938), the injection of extracts containing thyrotropic hormone prevents the following effects of the prolonged administration of oestrin to mice: (1) the spontaneous development of mammary carcinoma in a special strain of mice with a high, spontaneous incidence, (2) the development of the mammary gland in male mice, and (3) alterations of the anterior pituitary, likewise caused by oestrin, such as marked congestion and disappearance of the oxyphils.

Oehme (1936) concluded that one adrenal cortical extract ("Cortidyn"), but not a second called "Pancortex," prevents the elevation of basal metabolism due to thyrotropic hormone. However, the histological signs of thyroid stimulation appeared as usual. The effect observed appeared not to be due either to ascorbic acid or to tyrosine.

An increased rate at which isolated strips of the auricle beat can be observed, if guinea pigs receive injections either of thyroxine or of thyrotropic hormone (Ferrannini, 1936). From observations of the heart rate in rabbits, Rihl, Oestreicher, and Reiss (1936) concluded that the effects of thyroxine are strikingly different from those of thyroid hormone

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[14] The similar injection of progesterone as 1 Clauberg-unit daily was found to have no effect.

secreted in response to the injection of thyrotropic hormone. After the injection of the latter, the heart rate begins to rise within an hour and is 30–50 per cent more rapid after 7–9 hours. On the other hand, even after 4 mg. of thyroxine the heart rate is not significantly changed within a day. The authors' other comparisons of the effects of repeated doses appear to be less significant. Page and Sweet (1937) produced hypertension in dogs by means of Goldblatt's clamp. After hypophysectomy the blood pressure fell but could be raised moderately by the daily administration of 0.8 gm. of desiccated thyroid. The authors suggest that the lack of thyrotropic hormone following the removal of the hypophysis may account partly for the fall in blood pressure in dogs with experimental hypertension.

Anderson and Alt (1937) found that the addition of thyrotropic hormone to slices of isolated canine thyroid increased the oxygen-consumption of the tissue 17–120 per cent per hour during the first 3 hours; a similar change could not be produced if isolated slices of liver or kidney were used. These observations confirm the earlier report of Eitel, Krebs, and Loeser.

Either thyrotropic hormone or thyroid extract brings about a reduction in the concentration of hepatic glycogen. This effect appears not to be modified by the administration of KI (Holden and Thurston, 1935). Another action on carbohydrate metabolism attributed to the thyrotropic hormone is an increased rate of liberation of insulin in dogs, whether or not the vagi have been cut (Zunz and La Barre, 1935). Confirmatory experiments were performed in non-anesthetized dogs by Kotchneff and London (1937), who concluded that the concentration of insulin in the blood may be quadrupled 30 minutes after the injection of extract containing 20–60 units of thyrotropic hormone. There appeared to be no effect on the rate of liberation of epinephrine. After the repeated injection of thyrotropic hormone into guinea pigs, the heart undergoes considerable hypertrophy (about 60 per cent in

excess of its initial weight); coincidently, the concentration of glycogen is reduced to about one-fourth its former value (Lederer, 1935). Both of these effects can be observed after the basal metabolic rate has returned to normal but are less pronounced as the rate falls below normal with continued injection of the extract and the probable formation of "antihormone."

The metabolism of proteins or of substances related to proteins is referred to in a few reports.[15] Schönholzer (1937) fed casein to rats and relied upon the Unna-Pappenheim histological technic for recognizing protein in the liver. The injection of 100–300 units of thyrotropic extract for 1–7 days was followed by markedly diminished numbers or almost a complete absence of the *Eiweissschollen* (but see also the report of Liang and Wu [1937], who considered that a special hormone is responsible for such effects). According to Bühler (1935), thyrotropic hormone, by its action on the thyroid, increases the rate of excretion of creatine and creatinine in the dog but not in the rabbit. Maloberti (1936) believed that an increase in the concentration of glutathione in the blood and certain tissues of the guinea pig parallels the symptoms of hyperthyroidism provoked by the injection of thyrotropic hormone. Maloberti's results often were variable and would be more convincing if he had secured more supporting data.

Pugsley (1935) reported that thyrotropic hormone causes a fall of approximately 35–50 per cent in the concentration of serum-cholesterol in both rats and dogs. Injections were made intraperitioneally, sometimes twice daily for as long as 8–10 days. Only total cholesterol was determined. The effect could not be produced in one dog after thyroparathyroidectomy. Rothschild and Staub (1935) were not able to detect any effect of thyrotropic hormone on the lipoids of the blood of rabbits.

The relationship of the anterior pituitary, the thyrotropic

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[15] For reports dealing with the specific dynamic response in patients, see Sylla (1935) and Mahaux (1936).

hormone, and the thyroid gland to the metabolism of water is discussed in chapter x.

In the immature guinea pig the administration of a large dose of vitamin A (1,800 units daily for 10 days) prevents the action of 6 guinea pig units of thyrotropic hormone (Fellinger and Hochstädt, 1936).[16] Elmer, Giedosz, and Scheps (1935) concluded that both vitamin A and ascorbic acid inhibit the action of thyrotropic hormone in the guinea pig but are much less effective than iodide. Vitamin D appeared to be without action.[17]

According to Eitel and Lexer (1936), the healing of bone fractures in rabbits is facilitated by the administration of thyrotropic hormone or thyroid extract.[18] Likewise the healing of wounds in guinea pigs takes place at a faster rate, if thyrotropic hormone be administered (Eitel and Riecker, 1936). Arsenic (as 0.003–0.3 mg. As_2O_3 per kg. rat for 20 days) or CO (as repeated exposure of guinea pigs to an atmosphere containing 0.5 per cent CO) was believed to bring about a reduction in the amount of thyrotropic hormone (Kampelmann, and Kampelmann and Schulze, 1937).

The metabolism of thyrotropic hormone.—Fellinger (1936) and Bodart and Fellinger (1936) have undertaken the assay of thyrotropic hormone in the blood of patients. Before the material was injected, an attempt was made to remove thyroid hormone which would be a source of interference with the assays, as they were performed in guinea pigs. The authors concluded that a positive histological response of the guinea pig's thyroid can be secured from the thyrotropic hor-

[16] The authors do not mention whether or not the presence of iodine in the vitamin-A preparation was excluded.

[17] Demole and Ippen (1935) stated that ascorbic acid can prevent death after a fatal dose of thyroxine.

The experiments of Loeser and Trikojus (1937) indicated that thyrotropic hormone does not alter to any important extent the concentration of ascorbic acid in the liver and the adrenals. The authors found that adrenal hypertrophy followed the long continued administration of thyrotropic hormone. This effect was not prevented by the administration of ascorbic acid.

[18] See also chap. ii.

mone in 5–8 cc. of blood. Generally the blood of patients with hyperthyroidism contained less hormone than normal; the findings were similar in patients thought to be suffering from hypothyroidism due to hypofunction of the anterior pituitary. On the other hand, the concentration of thyrotropic hormone in the blood of patients with hypothyroidism of purely thyroid origin or in that of patients with a pituitary tumor associated with an elevated basal metabolic rate was higher than normal. In investigating the thyrotropic hormone of serum, Hertz and Oastler (1936) relied upon an exceedingly specific test—i.e., the induction of histological signs of thyroid activity in hypophysectomized rats. Thyrotropic hormone was detected in the serum of 9 patients with myxedema, whereas none could be found in the serum of 5 normal individuals or of 7 patients with hyperthyroidism. Serum in doses of 1–2 cc. twice daily was administered intramuscularly for 5 days.

There is still controversy concerning the excretion of thyrotropic hormone in the urine. Antognetti and Geriola (1936) could secure no convincing evidence that thyrotropic hormone can be extracted from the urine of normal persons or of patients with Graves's disease or myxedema, whether spontaneous or resulting from thyroidectomy. In the work of Hertz and Oastler referred to in the preceding paragraph the detection of thyrotropic hormone in urine was also undertaken. The authors usually injected 5 cc. of urine twice daily for 5 days by an intramuscular route into hypophysectomized male rats. Thyrotropic hormone could be detected in the urine of patients with myxedema, whereas none could be found in the urine of patients with hyperthyroidism or in that of normal persons. Niţescu and Timuş (1938) agree that the hormone cannot be found in normal urine or in urine of patients with Graves's disease; however, they did detect thyrotropic hormone in the urine of an acromegalic with symptoms of hyperthyroidism. Grumbrecht (1935) believed that the urine of women past the menopause contains thyro-

tropic hormone; he performed assays in the rabbit by injecting the extract of urine intravenously.

Goiter was produced by Remington (1937) in rats by feeding a diet containing too little iodine. The effects of thyrotropic hormone were no less difficult to elicit in such rats than in normal rats. On the other hand, thyroids of rats, goitrous for unknown reasons, were found by Anderson and Collip to be abnormally sensitive to the thyrotropic action of anterior pituitary extract.

The effects of iodides will be considered in this section. Friedgood (1936) reported that the administration of sodium iodide caused a remission of the symptoms of hyperthyroidism in guinea pigs receiving anterior pituitary extract. He concluded that the remission resembled that produced in human beings with exophthalmic goiter or with the hyperthyroidism of early acromegaly. Weil and Bernheim (1936) made auto-transplants of the thyroid after total thyroidectomy in the guinea pig. The effect of 70–400 units of thyrotropic hormone, indicated by histological signs of stimulation of the thyroid, could be antagonized by the administration of KI; however, a much greater antagonistic action was produced by thyroxine and, to a less extent, by diiodotyrosine. The results of Anderson and Evans (1937) were different from those of the authors just cited. Anderson and Evans concluded that the coincident administration of KI does not interfere with the production of thyroid hyperplasia by thyrotropic hormone but that the iodide prevents the liberation of thyroid hormone into the blood, so that a calorigenic effect does not appear. This conclusion was based on experiments in normal guinea pigs and hypophysectomized rats.[19]

Extracts containing thyrotropic hormone in relation to anti-hormone effects.—Some authors believe that a small amount of antithyrotropic substance is present in normal serum

[19] See also Franck's interpretation (1937) of histological changes in the pituitary after the injection of anterior pituitary extract with or without Lugol's solution or diiodotryosine.

(Herold, 1934; Scowen and Spence, 1936); however, this appears doubtful and was not confirmed by Rowlands and Parkes (1936). Various investigators[20] have experienced no difficulty in confirming earlier experiments on the production of thyrotropic antihormone; even with the best extracts available, repeated injections soon appear to lose their thyroid-stimulating properties, as is shown by the absence of anatomical signs of thyroid stimulation and of physiological changes, such as an increased basal metabolic rate due to the increased liberation of thyroid hormone. The serum of blood removed at this time prevents the thyrotropic action of anterior pituitary extract. Sometimes the antihormone effect appears to be specific for the animal species furnishing the pituitary tissue from which the extract was made (Eichbaum and Kindermann, 1936; Oudet, 1937); in other experiments, as in those of Thompson (1937), there seems to be no species specificity, and the serum alone seems to cause atrophic changes in the thyroid which resemble the condition following hypophysectomy. An intermediate phenomenon was described by Oudet, who concluded that species specificity is present after a short course of injections but not after a long course. A later report by Eichbaum and others (1937) suggested that two types of antibody are formed—one characteristic of the proteins of the species, the other characteristic of thyrotropic hormone.

Loeser (1936) has confirmed earlier experiments indicating that hypophysectomy does not interfere with the formation of thyrotropic antihormone. He continues to affirm (Eitel and Loeser, 1935; and Loeser, 1936) that the presence of the thyroid gland greatly facilitates the formation of antihormone; but this is improbable and could not be confirmed either by Oudet (1936) or by Chou (1937).

Okkels' experiments (1937) likewise indicate that tissues

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[20] Extracts with thyrotropic effects were used in a number of the experiments discussed in chap. iii.

other than the thyroid are sources of antihormone and that the neutralization of thyrotropic hormone does not occur in the thyroid. After anterior pituitary extract had been injected into rabbits for 2 months and the thyroid was then refractory toward further treatment, the gland was removed and, presumably still living, was perfused by the Carrel-Lindbergh technic with normal serum containing anterior pituitary extract. Thyroid-stimulating effects could be observed within 24 hours. In other experiments the author was surprised by the fact that a large volume of rabbit serum containing antihormone only partially neutralized the thyrotropic action of anterior pituitary extract with which it was mixed. The mixture was perfused through the isolated thyroid of the normal rabbit.

Werner's experiments (1936) strongly support the view that thyrotropic antihormone is an artifact characteristic of relatively crude anterior pituitary extracts. Equivalent doses (in terms of weight of crude gland) of extract of the beef anterior pituitary were injected into guinea pigs and led to the following conclusions: (1) whether or not antihormone is produced depends on the type of extract not on its potency, (2) it may be possible to produce antihormone by doses of extract without thyroid-stimulating effects, (3) the thyroids of animals completely refractory to one extract may be readily stimulated by the other—yet both were obtained from ox pituitary—and (4) an extract may cause the formation of no antihormone in the majority of animals even after injection for nearly 3 months. As a basis for these conclusions the author relied upon the basal metabolic rate and the histology and total iodine-content of the thyroid.

The assay of thyrotropic hormone.—Among mammals no animal is as convenient for the assay of thyrotropic hormone as the immature guinea pig. The histological signs of thyroid stimulation—vacuolization of the colloid, hypertrophy, and later, hyperplasia (increased mitotic division) of the epithe-

[194]

lial cells—were first investigated by Aron and Loeb[21] and have been extensively used as a means of assay. According to Wilcke (1935), fixation is of great importance, if an attempt is made to grade the histologic effects by the plan of Heyl and Laqueur; Wilcke recommended 10 per cent formalin as a fixative. The production of thyroid hypertrophy as a means of assay (Rowlands and Parkes) is more objective but requires much larger doses of hormone. There is no confirmatory evidence to support the contention of Heyl and Laqueur that a different principle is responsible for hypertrophy.

Smelser (1937) recommended the use of day-old White Leghorn chicks. His practice was to divide the total dose into five daily injections and to perform the necropsy 24 hours after the last injection, when the thyroid lobes were dissected out under a binocular microscope. The method was found to be more sensitive than a similar technic applied in guinea pigs.

Other methods which may be sensitive are either inconvenient or are difficult to evaluate. For example, the decrease in the total amount of iodine in the thyroid of chicks or guinea pigs as a result of thyroid stimulation is a method suggested by Cuyler, Stimmel, and McCullagh (1936) and Stimmel, McCullagh, and Picha (1936). Atwell (1935) recommended the hypophysectomized tadpole as a very sensitive biological indicator; the prominent change which occurs if thyrotropic (or thyroid) extract is administered is metamorphosis. Collip and his collaborators have frequently detected the presence of thyrotropic hormone by its calorigenic action in hypophysectomized rats.

The chemistry of thyrotropic hormone.—Thyrotropic hormone is available only as an impure extract. It is a heat-sensitive substance which, like other anterior pituitary hormones, appears to belong to the group of proteins. Readers interested in a new report on the preparation of extract are referred to the article of Lambie and Trikojus (1937). There

[21] The following are late reports by these authors: Kippen and Loeb (1935) and Aron (1936).

are no new experimental data enabling us to decide whether or not thyroid stimulation in amphibian larvae is due to a principle different from that stimulating the mammalian thyroid.

SUMMARY

The recent investigations of the various aspects of the biology of the thyrotropic hormone have yielded a disappointingly small crop of new facts. Much of the effort has been expended in consolidating or extending slightly knowledge which was already available.

Probably there is general agreement on the principal functions of the thyrotropic hormone. Its importance is great in nearly all classes of vertebrates—i.e., to insure normal thyroid function, especially the discharge of thyroid secretion. Unless thyroid hormone is actually liberated from the gland, various striking effects occur in cold-blooded animals—i.e., the metamorphosis of tadpoles cannot take place; in both urodele and anuran amphibia molting or the desquamation of cornified epidermis is absent; on the other hand, in reptiles molting may either be accelerated or take place less frequently. In both classes of animals, as in mammals, the rate of heat-production is abnormally slow and cannot be adapted readily to the demands of the environment. Atrophy of the thyroid gland may or may not rapidly appear after hypophysectomy. The invariable effect of the operation is to produce all the histological signs of inactivity of the thyroid, such as the accumulation of densely staining colloid in vesicles lined by flat epithelium, together with physiological evidences of thyroid deficiency, such as a low rate of metabolism.

Changes in the opposite direction are readily produced by the injection of extracts of the anterior pituitary. The colloid becomes vacuolated and may almost disappear. The epithelium, now active, is cuboidal or columnar and begins to proliferate. Animals of various classes exhibit changes dependent upon thyroid secretion. Metamorphosis can be pro-

duced in hypophysectomized anuran larvae. Adult amphibia, subjected to the same operation, shed the accumulated layers of cornified epidermis. Heat-production is raised to normal or can be elevated above normal.

These facts have led to efforts to attribute deficiency or hyperfunction of the thyroid in man to a deficient or abnormally rapid rate of secretion of thyrotropic hormone. Such an explanation, it appears, may be of value in unraveling the genesis of certain types of hyperthyroidism in man. The hyperthyroidism associated with acromegaly probably is the result of the secretion of excessive amounts of thyrotropic hormone. On the other hand, thyroid deficiency in man less often seems to depend upon a disturbance of the anterior pituitary.

The effects of anterior pituitary extracts containing thyrotropic hormone have been studied extensively in mammals. Occasionally all the histological signs of thyroid stimulation are present without the expected general physiological changes, such as an elevated basal metabolic rate. Usually, however, the phenomena are associated. Under suitable conditions thyroid hormone is found to be liberated within a few hours or less following the injection of thyrotropic extract and acts more rapidly than its essential fraction, thyroxine. Antagonistic substances such as oestrogens, thyroxine, iodides, etc., appear to act in a variety of ways. Sometimes the action is peripheral to the thyroid; at other times the thyroid itself or the interaction between thyrotropic hormone and the thyroid appears to be affected.

Thyrotropic extracts contain both the hormone and other substances. If such extracts are repeatedly injected, "antihormone" may be produced. This phenomenon has not been shown to be of physiological importance.

Exophthalmos can be produced by the injection of anterior pituitary extract into normal or thyroidectomized animals. It is not known whether or not thyrotropic hormone is responsible for its appearance.

THE INTERRELATIONSHIP BETWEEN THE PARS
GLANDULARIS AND THE ADRENAL GLANDS;
THE INFLUENCE OF THE PARS GLANDULARIS
ON THE METABOLISM OF CARBOHYDRATES,
LIPOIDS, PROTEINS, AND MINERALS (WITH RE-
MARKS ON THE PITUITARY-PARATHYROID IN-
TERRELATIONSHIP)

NUMEROUS interrelationships between the anterior
pituitary and the adrenal glands have been sug-
gested or investigated in almost every field of in-
terest to the endocrinologist. Much of this work is discussed
elsewhere and, for complete references, the reader is referred
to the Index. The review in this section will be principally
confined to a discussion of the part taken by the anterior
pituitary in preserving the function of the adrenal cortex as
demonstrated by the morphology of that structure. The
important interrelationships affecting the metabolism of car-
bohydrates and fats are taken up in the sections dealing with
the metabolism of these foodstuffs.

It is well known that the cortex of the adrenal glands
undergoes a pronounced atrophy after hypophysectomy,
whereas the medulla is affected scarcely at all. Likewise ex-
tracts of the anterior pituitary affect the cortex chiefly, if not
entirely. Therefore, almost all the discussion will refer to the
adrenal cortex.

*New observations on the effects of hypophysectomy or of an-
terior pituitary extract*[1] *on the morphology of the adrenal glands.*
—Adrenal cortical stimulating hormone is probably as wide-

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[1] No short, unobjectionable term to describe the hypothetical adrenal cortical
stimulating hormone has been devised. Such terms as "adrenotropic" and "corti-
cotropic" are undesirable from an etymological standpoint.

ly distributed as other hormones of the anterior pituitary. Leonard (1937) concluded that it is present in the pituitary of the fowl. According to the assays of McQueen-Williams (1935) in rats, the anterior pituitary of the ox contains a higher concentration of adrenal cortical stimulating hormone than that of the rat. The author's preliminary experiments indicated that the removal of both adrenal glands is followed by an increase in the amount of the hormone in the pituitary.

Extracts of the anterior pituitary readily cause enlargement of the adrenal glands of normal or hypophysectomized animals chiefly by bringing about hypertrophy of the cortex. The effects of extracts in normal animals are, of course, difficult to evaluate accurately because the pituitary is intact. Among such observations are those of Bierring (1935), Friedgood (1936), and Latyszewski (1937) who used rats, guinea pigs, and rabbits. Bierring, who injected crude anterior pituitary extract into rats—sometimes for months— considered that the important effect is on the zona glomerulosa but that the three cortical zones were more clearly demarcated in the treated animals. Some of Moon's observations (1937) also were made in normal rats. He reported that cells of the glomerular and fasciculate zones underwent both hypertrophy and hyperplasia after the injection of extract. In the guinea pig, according to Friedgood, the left adrenal undergoes more hypertrophy than the right. Latyszewski did not feel convinced that the changes he observed in the guinea pig and rabbit after the injection of extract were specific or easily reproducible. The principal effects he described were in the zona fasciculata and consisted of the loss of lipoids and cellular hypertrophy affecting both the protoplasm and the nuclei.

The effects of extracts in hypophysectomized animals are more easily analyzed, because normally secreted cortical-stimulating hormone is not an unknown and therefore con-

fusing factor.[2] Davidson (1937) produced a marked hypertrophy of the adrenal glands in hypophysectomized rats by injecting anterior pituitary extract. He concluded that the cortical enlargement was due to cellular hypertrophy, not hyperplasia. The histological appearance of the cortical lipoids has received the special attention of Reiss and others (1936) and of Moon (1937). In normal rats there exists a narrow band of tissue between the zone fasciculata and the zona glomerulosa, which histologically appears to contain little or no lipoid. Deposition of lipoids in the cells of this band is one of the earliest signs of a cortical-stimulating effect (Moon). After hypophysectomy the outer part of the zona fasciculata[3] rapidly loses its lipoids, which are specifically restored by the injection of pituitary extract containing adrenal cortical stimulating hormone (Reiss and others; Moon).

The development of the "X-zone" of the mouse adrenal, located as a central fringe of the cortex, appears to depend on sex, inasmuch as it is found in immature or young female mice, whereas it fails to develop in male mice unless castration is performed. Deanesly (1938) suggested that the development of the X-zone probably depends upon a secretion of the anterior pituitary. She found that the castration of mice with hereditary dwarfism and with partial pituitary deficiency is not followed by the development of an X-zone.

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[2] Cutuly (1936) studied quantitatively the morphology of the adrenal glands of rats 30 days after hypophysectomy. At death, the male rats weighed an average of 166 gm., the female rats, 139 gm. Atrophy appeared to be due solely to cortical shrinkage and was relatively greater in female rats. His results were as follows (the figures refer to the mean of the calculated weights in milligrams):

Part	Cortex		Medulla*	
Sex	♂	♀	♂	♀
Normal rats	23.07	37.06	2.53	3.44
Operated controls	24.63	38.89	3.17	3.71
Hypophysectomized rats	7.83	10.24	2.00	1.96

* Differences in weight not statistically significant.

[3] Moon's Fig. 3 indicates that this does not represent a widening of the lipoid-free band of normal animals.

Lacassagne and Raynaud (1937) stated that, although oestrone or oestradiol do not disturb the development of the X-zone, these oestrogens do cause regressive changes in the adrenals, e.g., loss of lipoids. The regressive changes were attributed to an interference with pituitary secretion.

Several reports on the morphology of the adrenal cortex in relation to the pars glandularis also mention the medulla. In Cutuly's quantitative morphological study (1936) of the adrenals of normal and hypophysectomized rats of both sexes the mean weight of the medulla of operated rats was less than that of control animals. However, the difference was not statistically significant. Davidson (1937) stated that after the injection of adrenal cortical stimulating extract into hypophysectomized rats the medulla appeared more normal. Specifically, he mentioned the absence of vacuoles, which sometimes appeared in the adrenal medulla of operated, non-treated rats. Normal rats received daily injections of a crude anterior pituitary extract for as long as 9 months in the experiments of Bierring (1935). He reported that the medulla appeared hyperplastic and that enlarged chromaffin cells were crowded with granules. The changes observed by this author are the reverse of those attributed by Anselmino and Hoffmann to medulla-stimulating ("adrenotropic") hormone. The observations do not offer convincing evidence that the pars glandularis has an important influence on the morphology of the adrenal medulla.

Physiological and pharmacological correlations.—Grollman and Firor (1935) used several methods to produce chronic adrenal insufficiency in rats, cats, and dogs. They concluded that if no attempt was made to treat the cortical deficiency for a considerable time, adrenal cortical extract could not cause a resumption of growth, a reappearance of normal sexual performance, or the maintenance of a normal body-temperature. The lack of benefit of adrenal cortical hormone under such conditions was attributed to irreparable damage of the pars glandularis; for anterior pituitary extract repaired

the defects. Early treatment by cortical hormone prevented pituitary damage, i.e., the defects of growth, gonadal function, and metabolism did not appear. In the experiments of Gaunt, Remington, and Schweizer the metabolism of water after the intraperitoneal injection of isotonic glucose solution was investigated. At least in respect of the ease with which "water intoxication" was produced or ameliorated or prevented by cortical extract, it appeared that hypophysectomized rats suffered from a deficiency of adrenal cortical hormone.

All recent work indicates that thyroidectomy interferes neither with the release of adrenal cortical stimulating hormone from the pituitary nor with the peripheral action of the hormone. Cortical-stimulating hormone produces about the same adrenal hypertrophy and increased accumulation of osmiophilic material in the cortical cells of tadpoles, whether or not the thyroid is present (Atwell, 1937). Thyroidectomy appears not to affect the adrenal-stimulating effects of anterior pituitary extract in guinea pigs (Jores and Boecker, 1937).[4] Compensatory hypertrophy of an adrenal gland after the removal of its mate depends upon the liberation of adrenal cortical stimulating hormone from the pituitary; however, thyroidectomy does not interfere with this phenomenon in the male rat (Winter and Emery, 1936).[5]

[4] These authors found that adrenal hypertrophy following the administration of thyroxine was associated with a loss of lipoids from the cortex. This effect, of course, is the reverse of that considered to be typical of adrenal cortical stimulating hormone.

[5] These authors found that gonadectomy does not interfere with compensatory adrenal hypertrophy in rats of either sex. If both adrenals are intact, castration is followed by adrenal hypertrophy, spaying by adrenal atrophy.

Elmer, Giedosz, and Scheps (1937) concluded that thyrotropic hormone played the important part in the adrenal hypertrophy which follows the administration of acid extract of the anterior pituitary, because the effect was prevented by the administration of iodide. Friedgood (1936) also administered iodides and alkaline anterior pituitary extract to guinea pigs and found that adrenal hypertrophy and splenomegaly were less pronounced or even absent. However, Friedgood did not feel that the hypothesis that thyrotropic hormone is responsible for the cortical-stimulating effects of pituitary extract is warranted.

Perla (1935–36) and Perla and Rosen (1935) have reported new experiments indicating that the increased toxicity of histamine in hypophysectomized rats is due to a deficiency of adrenal cortical hormone resulting from the absence of cortical-stimulating hormone. According to Selye and Collip (1936), large doses of oestrone or the administration of formaldehyde bring about hypertrophy of the adrenal cortex of the rat. These changes appear to be due to the increased liberation of adrenal cortical stimulating hormone, because they cannot be produced in hypophysectomized rats.

Some aspects of the metabolism of adrenal cortical stimulating hormone.—Several authors have shown that the pars glandularis must be intact if compensatory hypertrophy of an adrenal is to take place after the other has been removed. Reiss, Bálint, and Aronson (1936) found that compensatory hypertrophy amounts to about 95 per cent if partial hypophysectomy has been performed, whereas in normal animals the compensatory hypertrophy is only 20 per cent. Apparently operative trauma is followed by changes facilitating the formation or liberation of adrenal cortical stimulating hormone. The adrenal cortices of the female rat are considerably larger than those of the male. This suggests that the female pituitary liberates more cortical-stimulating hormone than the male. This hypothesis was tested by Wyman and tum Suden (1937) by determining the survival of homotransplants. Regeneration of such transplants occurred in 71 per cent of female recipients but in only 20 per cent of male recipients. The sex of the donor appeared not to affect the results. These authors also showed (1937) that the successful transplantation of the adrenal requires pituitary secretion. The adrenal of the hypophysectomized rat can be successfully transplanted into a normal rat. Regeneration of a transplant is particularly favored by adrenal insufficiency (Wyman and tum Suden, Ingle and Higgins), probably because the rate of formation and liberation of cortical-stimu-

lating hormone is accelerated.[6] On the other hand, the rate of secretion of cortical-stimulating hormone is so diminished as a result of the administration of adrenal cortical extract that cortical atrophy appears but can be prevented, if cortical-stimulating extract be simultaneously administered (Ingle and Kendall, 1937).

In human beings with increased intracranial tension, usually the result of primary cerebral tumors, Kraus (1937) observed a hyperplasia of the pars glandularis associated with a similar change in the cortex of the adrenal glands, including an increased accumulation of lipoids.[7] Kraus believed that the cortical hyperplasia was due to an increased secretion of adrenal cortical stimulating hormone by the anterior pituitary and described the phenomena as "corticotropic hyperpituitarism." He pointed out that cortical atrophy occurs in the pituitary cachexia of Simmonds. The reports of Giordano and Zeglio (1936) were available only in the form of abstracts. These authors reported that adrenal cortical stimulating hormone, recognized by its effect on the adrenal of the guinea pig, can be extracted from the urine of patients with hypertension. They believed that effects of urinary extracts on the adrenal medulla could be detected but were less important.

The chemistry and assay of adrenal cortical stimulating hormone.—Little is known concerning the chemistry of cortical-stimulating hormone. Although incidental observations on the extraction and some properties of potent extracts are mentioned in several reports, it appears that little is to be gained from a review at this time. One method of extraction which should be cited is that of Moon (1937), who reported that by Lyons' method of preparing lactogenic extract the material which is insoluble at pH 6.5 is rich in cortical-stimulating hormone. Extract rich in lactogenic hormone is, by this method of extraction, least soluble at pH 5.5.

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[6] See also McQueen-Williams (1935).

[7] The weight of the adrenal glands was 30–40 per cent greater than normal.

The methods which have been used for the assay of adrenal cortical stimulating extract have received no careful quantitative study. Unquestionably, hypophysectomized animals should be used, if there is to be the least possible doubt as to the specificity of the effects. Reiss and others (1936), Collip (1937), and Moon (1937) have all used hypophysectomized rats for assay and usually have relied upon both the gross change—hypertrophy—and microscopic evidences of repair—especially the reappearance of lipoids distributed generally. Methods based upon the use of normal mice or rats have been described by Jores and Beck (1936) and by Moon (1937).

THE METABOLISM OF CARBOHYDRATES IN RELATION TO THE PARS GLANDULARIS

Great interest in the importance of the pituitary body in carbohydrate metabolism was aroused by Houssay and Biasotti, who discovered that the course of diabetes following pancreatectomy in the dog is greatly ameliorated by removal of the hypophysis. Without doubt the extirpation of the pars glandularis is responsible for this change. The problem, in general terms, is: How and to what extent is the metabolism of carbohydrates regulated by the pars glandularis? Numerous aspects of this problem have been studied, especially since 1934. However, it will be seen that our knowledge of the mechanisms in operation is still regrettably limited.

The metabolism of carbohydrates after hypophysectomy.—Previous work had demonstrated several important changes consequent to hypophysectomy—i.e., the blood sugar of fasting animals falls to abnormally low levels; the sensitivity toward insulin is greatly increased; the regulation both of the absorption of glucose and of the formation and degradation of glycogen is disturbed.

If animals are fed adequate amounts of carbohydrate, the concentration of sugar in the blood is not strikingly different

in hypophysectomized animals from that in normal animals. Shortly after food is withheld, however, a marked hypoglycemia appears in successfully operated animals. For example, Russell (1936) found that the concentration of sugar in the blood of young male rats, 3–4 weeks after hypophysectomy, was reduced approximately 50 per cent after a fast of 8 hours, whereas the reduction occurring in normal rats was only 20 per cent. If the fast was continued for 10 hours longer (total 18 hours) a greater change then occurred in normal
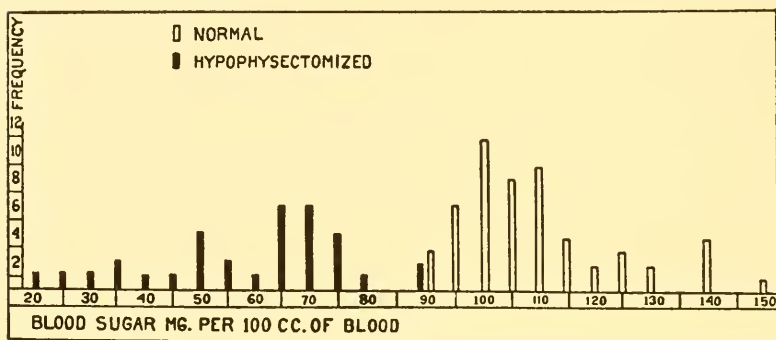
FIG. 23.—The concentrations of sugar in the blood of normal and hypophysectomized monkeys in relation to their frequency. The monkeys were first starved 16–18 hours. (From Smith, Dotti, Tyndale, and Engle, Proc. Soc. Exp. Biol. Med., **34,** 247–49 [1936].)

rats (total reduction, 32 per cent) than in hypophysectomized animals (total reduction, 54 per cent). The results of the withdrawal of food are similar in the rabbit (Cope, 1937) and monkey (Smith and others, 1936). Figure 23 illustrates the distribution of concentrations of sugar in the blood of normal and hypophysectomized monkeys, as determined by Smith, Dotti, Tyndale, and Engle after the animals had been fasted for 16–18 hours. The concentration of sugar in the blood of partially hypophysectomized monkeys was found to lie (87 ± 2.7[8] mg. per cent) between that of normal monkeys (110 ± 2.0[8] mg. per cent) and that of hypophysec-

[8] Standard error of the mean.

tomized monkeys (59 ± 3.1[8] mg. per cent).[9] The reasons for the precipitate diminution of the sugar of the blood of hypophysectomized animals as a result of fasting will be discussed later.

The rate at which glucose is absorbed from the digestive tract by hypophysectomized animals is abnormally slow, as was first demonstrated by Phillips and Robb in rats. Bennett (1936), Fisher and Pencharz (1936), Russell (1937), and Russell and Bennett (1937) all used rats and agree with the conclusion of Phillips and Robb. According to Bennett, the amount of glucose absorbed in an arbitrary period is about 35 per cent less in hypophysectomized than in normal rats. Russell and Cori (1937) reported that the tolerance for intravenously injected glucose is reduced in hypophysectomized rats to the same extent that oxygen-consumption suffers a reduction.[10] The renal threshold of glucose was found to be abnormally high in operated rats. Russell and Bennett found that as early as 24 hours after hypophysectomy,[11] fasting is followed by an abnormally rapid decrease in the concentration of glucose in the blood and of glycogen in the liver and striated muscle. If such animals are then fed, the return of these carbohydrates to normal levels is abnormally slow, principally because the reserves are abnormally low and because the absorption of glucose is abnormally slow.

[9] Scott (1937) investigated the concentration of lactic acid in the blood of normal and hypophysectomized monkeys and obtained high values, which she attributed to muscular activity which was beyond her control. Blood obtained from the heart of normal monkeys contained 104 ± 6.5 mg. per cent of lactic acid, whereas similar blood of hypophysectomized monkeys contained 37 ± 4.5 mg. per cent.

See the article of Marenzi (1936) for an account of the changes in, and the effects of pituitary (extracts) on, the following constituents of striated muscle of the toad after hypophysectomy: glycogen, inorganic P, phosphocreatine, glutathione, and lactic acid.

[10] There are few new data on changes in glucose-tolerance as a result of hypophysectomy. For example, Slome (1936) found that glucose-tolerance is increased after hypophysectomy in the toad, *Xenopus laevis*. There are other references in the text.

[11] Inanition or brain injury or the absence of the pars neuralis was not responsible for the change.

After hypophysectomy, rats continue to oxidize glucose readily. In fact, when such animals depend upon their own reserves of foodstuffs, as in fasting, they depend to an unusual extent on carbohydrate-oxidation for their energy requirements (Fisher and Pencharz, 1936). Fisher and Pencharz also found that if hypophysectomized rats are fed glucose, they oxidize more carbohydrate to supply energy than do normal rats, despite the fact that the rate of oxygen-consumption and of absorption of glucose is lower after hypophysectomy.[12] A high-fat diet prior to glucose feeding appeared to lessen the oxidation of glucose only slightly. Greeley (1935) attempted to determine the rate of utilization of glucose by hypophysectomized rabbits at the time of maximum need during fasting. He considered that such a need occurred 5–8 hours after a drop in blood sugar appeared (11–32 hours of fast) in fasting hypophysectomized rabbits. He concluded that at least 0.50–0.67 gm. of glucose per kg. body-weight per hour is required by an intravenous route, if the blood sugar is to be maintained near (usually below) the normal level. Russell (1937) investigated the action of thyroxine on the metabolism of glucose by hypophysectomized rats. From comparisons with operated animals receiving glucose alone, she concluded that thyroxine causes an increase in the rate of absorption of glucose and in the rate of oxidation of glucose, roughly proportional to the increase in oxygen consumption caused by the hormone.

According to Weichselbaum, Heinbecker, and Somogyi (1937), tolerance toward glucose is improved in hypophysectomized dogs by a high-carbohydrate diet compared with a high-fat diet. The diets did not uniformly cause this sort of a difference in normal dogs. These authors also found (Somogyi, Weichselbaum, and Heinbecker, 1937) that hyperglycemia following hypoglycemia due to the administration

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[12] During the first 4 hours after the feeding of glucose, normal rats might oxidize 144 mg. of the sugar per 100 gm. body-weight in comparison with 190 mg. per 100 gm. body-weight in hypophysectomized rats.

of either glucose or insulin appeared both in normal and in hypophysectomized dogs.

Abnormalities in the deposition and degradation of glycogen in hypophysectomized animals have already been referred to briefly. Bennett (1936) as well as Russell (1936) determined the concentration of sugar in the blood and of glycogen in the liver and striated muscle of normal and hypophysectomized rats under various conditions. After a fast of 8 hours, the operated rats metabolized much more of the glycogen of the liver (95 per cent compared with 27 per cent in normal rats) and of striated muscle (24 per cent compared with 8 per cent). If the fast was prolonged to 18 hours, both normal and operated animals had consumed most of the hepatic glycogen, whereas a further loss of muscle glycogen occurred only in hypophysectomized rats. These observations were made by Russell, who also reported that the chief abnormality found in hypophysectomized rats fed 2 gm. of starch within 8 hours after a fast of 18 hours was a low concentration of glycogen in the liver. Likewise, after the feeding of glucose, partly because of slow absorption, hypophysectomized rats restore the glycogen of the liver and striated muscle only slightly (Bennett). Bennett's results are summarized in Table 6. His calculations of the proportion of absorbed glucose converted into glycogen indicated that the percentage so converted is much higher in normal animals—especially in respect of hepatic glycogen. Cope (1937) has reported further experiments in rabbits from which he concluded that hypophysectomy interferes with the endogenous formation of carbohydrate and that when hepatic glycogen is exhausted, the concentration of sugar in the blood rapidly falls to levels associated with the onset of convulsions so that the animal, in this respect, behaves like a hepatectomized animal. In the hypophysectomized animal the hepatic glycogen appears to be only of exogenous origin. According to Soskin and others (1935), the hypophysectomized dog,

unlike the normal, cannot form carbohydrate from fat.[13] Ketonuria does not appear readily in hypophysectomized-depancreatized dogs even in the presence of hyperglycemia and glycosuria. The authors concluded that glucose can be endogenously derived only from carbohydrate and protein after hypophysectomy. Crandall and Cherry (1937) likewise

TABLE 6

CARBOHYDRATE METABOLISM IN NORMAL AND IN
HYPOPHYSECTOMIZED RATS*

ALL RATS FASTED FOR 24 HOURS	GLUCOSE ABSORBED	GLUCOSE IN BLOOD	GLYCOGEN IN	
			Liver	Striated Muscle
	Mg. per 100 Gm. Body-Weight in 2 Hours	Mg. Per Cent	Mg. Per Cent	Mg. Per Cent
Normal..............................	....	80	23	502
Hypophysectomized.....................	....	51	15	322
After administration of 2.5 cc. 35 per cent glucose to normal....................	412	140	1,348	673
After similar treatment of hypophysectomized..............................	247	111	194	378

* From Bennett, Proc. Soc. Exp. Biol. Med., **34**, 277–79 (1936).

performed experiments with dogs and believed that their results indicated that the formation of glucose from one amino-acid, glycine, is not prevented by hypophysectomy. The technic of their experiments is described in the section dealing with the effects of insulin.[14]

The recent experimental work so far reviewed, as well as

[13] However, even in normal dogs, it is not generally believed that proof of the formation of carbohydrate from fat, other than glycerol, is available.

[14] According to Schott, Samuels, and Ball (1937), the Walker tumor No. 256 in male rats contains significantly more glyocgen (but grows more slowly) in hypophysectomized than in normal rats. The amount of glycogen in the tumor of rats was: (1) 4 hours after feeding: normal, 0.026 per cent; hypophysectomized, 0.046 per cent, and (2) on high caloric diet: normal, 0.058 per cent; hypophysectomized, 0.186 per cent.

previous work, indicates that hypophysectomy leads to the following changes in the metabolism of carbohydrates.[15]

1. The rate of absorption of glucose is abnormally slow.

2. Fasting leads to an abnormally rapid utilization of glycogen both of the liver and of striated muscle. The more labile hepatic glycogen is more strikingly depleted. In the opinion of Fisher, Russell, and Cori (1937), a secretion of the pars glandularis regulates the (formation and) utilization of glycogen in fasting animals and spares carbohydrates so that fat and protein are utilized to a greater extent as sources of energy. This regulatory influence is lost after removal of the gland, so that carbohydrate oxidation continues at an abnormally rapid rate until even the concentration of sugar in the blood falls to low levels.

3. A further metabolic abnormality probably is an interference with gluconeogenesis from non-carbohydrate sources. It appears that the glycerol of fats cannot be used to form carbohydrate in hypophysectomized animals. The degree of disturbance of gluconeogenesis from proteins is not known with any accuracy. Apparently glycine can be utilized. Also, Fisher, Russell, and Cori found that the excretion of nitrogen in the urine is not affected by hypophysectomy. However, the G/N ratio of hypophysectomized dogs receiving phlorhizin is lower than normal and the quantity of N excreted is less (Houssay and others), which suggest a lowered rate of formation of glucose from protein.

4. All the foregoing changes help to explain the slow rate at which carbohydrate reserves are replenished when food is again furnished to fasting hypophysectomized animals. Absorption is slow; the reserves are low or, in the case of the liver, may be virtually exhausted; the animal continues to depend to an abnormal extent on carbohydrate-oxidation as a source of energy; and, finally, carbohydrate from non-carbohydrate sources can be secured only to a limited extent.

The effects of epinephrine in hypophysectomized animals.— So far as carbohydrate metabolism in normal animals is concerned, epinephrine appears to produce the following changes:

1. A hyperglycemia appears and persists. The increased concentration of blood sugar is partly due to increased hepatic glycogenolysis and partly due to diminished utilization of sugar by the tissues.

2. Simultaneously epinephrine promotes the formation of glycogen in the liver from lactic acid, the formation of which depends upon the degradation of muscle glycogen. In the formation of lactic acid from muscle glycogen, hexosemonophosphate must be formed; phosphate is therefore mobilized, and the concentration of inorganic P in the blood falls.

[15] The most numerous experiments have been performed with rats in which, as Fisher, Russell, and Cori emphasize, experimental procedures such as fasting may produce changes different from those observed in larger animals.

Therefore, the injection of epinephrine produces a hyperglycemia, a fall in the hepatic glycogen (which is restored later), a fall in the glycogen but an increase in the hexosephosphate of striated muscle, a fall in the concentration of inorganic P in the blood, and a change in the reverse direction of lactic acid. It is proposed to examine, in the light of new work, how these effects are modified by hypophysectomy.

Years ago Aschner learned that the subcutaneous injection of epinephrine produces glycosuria in hypophysectomized

TABLE 7

	Change as Mg. Per Cent in	
	Normal Rats	Hypophysecto-mized Rats
Sugar of blood after subcutaneous injection..........	+103	+ 38
Sugar of blood after intravenous injection...........	+ 68	+ 78
Hexosephosphate* of muscle after subcutaneous injection.....................................	+ 43	+ 13
Hexosephosphate* of muscle after intravenous injection.....................................	+ 53	+ 70
Glycogen of muscle after subcutaneous injection.....	−182	− 56
Glycogen of muscle after intravenous injection.......	−130	−158

* The figures refer to the concentration of hexose.

dogs much less readily than in normal animals. This observation applies with equal force to the behavior of the sugar in the blood and has been extended to other mammals. Deficient absorption as an important factor in explaining the small response was not considered experimentally until Russell and Cori (1937) undertook their work in rats. These authors observed changes after the injection of epinephrine into anesthetized rats as shown in Table 7. This brief summary of the results indicates that the delayed absorption of epinephrine from the subcutaneous tissues is of great importance in accounting for the apparent insensitivity of hy-

pophysectomized animals toward changes in carbohydrate metabolism caused by epinephrine.[16]

In all other work epinephrine was administered subcutaneously. Obviously, then, if observations were made in well-fed animals, differences in the reponse of normal and hypophysectomized animals cannot be attributed to a fundamental change in the action of epinephrine, unless the factor of deficient absorption has been ruled out. Cope (1937) and Cope and Thompson (1937) used rabbits. They believed that storage of hepatic glycogen does not follow the subcutaneous injection of epinephrine, but they did find in a different series of animals that the hormone causes an increase in the concentration of lactic acid in the blood comparable to that produced before hypophysectomy. (It appeared that less glycogen was formed by the liver from intravenously injected lactate as a result of hypophysectomy.) The lactic acid of the blood of hypophysectomized rats, which were fasted but received no epinephrine, began to rise when the concentration of sugar in the blood fell below 40 mg. per cent. Cope and Thompson believed that hypophysectomy does not affect the mobilization of the glycogen of muscle. Chaikoff and others (1935) used dogs for their experiments. They injected epinephrine subcutaneously and concluded that the response of hypophysectomized animals—in respect of increase in the concentration of sugar and lactic acid in the blood and of decrease in inorganic P—is indefinitely smaller than that of

[16] Heinbecker and Weichselbaum (1937) found that the intraperitoneal injection of epinephrine provokes hyperglycemia with equal effectiveness in normal and hypophysectomized dogs, provided that the nutritional condition is good.

Collip, Thomson, and Toby (1936) injected epinephrine subcutaneously and concluded that, as a result of hypophysectomy, hyperglycemia and reduction of muscle glycogen are prevented but that restoration of the effects appears if anterior pituitary extract be injected. The authors used rats. Bachman and Toby (1936) reported that hypophysectomy interferes with the mobilization of glycogen in muscle caused by the injection of epinephrine into rabbits. These authors injected the hormone subcutaneously but sometimes observed a satisfactory hyperglycemic response, if the liver contained an adequate amount of glycogen.

normal animals or of animals subjected to all the operative procedures except hypophysectomy.[17]

The effects of insulin in hypophysectomized animals.—It has long been known that, as a result of the extirpation of the pituitary body, sensitivity toward insulin is greatly increased. The change is due to the removal of the pars glandularis and not to removal of the pars neuralis (see the recent articles of Pencharz, Cori, and Russell, 1936; and of Karlik, 1936). However, Chaikoff, Reichert, Larson, and Mathes (1935) showed that retraction of the right temporal lobe of the dog (after craniotomy and incision of the dura mater) alone was sufficient frequently to increase insulin-sensitivity even 3 months after operation. There occurred in some animals as much fall in the concentration of sugar and inorganic P in the blood as in hypophysectomized animals. In the insulin-sensitive animals, in which operation had been carried only to the stage of temporal-lobe retraction, the pituitary appeared normal; however, the authors suggest that an unrecognized injury of the region about the pituitary had occurred. The quantitative studies of Heinbecker, Somogyi, and Weichselbaum (1937) indicated that in the dog insulin-sensitivity is approximately doubled 4 weeks after hypophysectomy and, after a year, is quadrupled.

From the discussion of the metabolism of carbohydrates in hypophysectomized animals it is clear that such animals tend rapidly to use up all available carbohydrate reserves when fasting is imposed, whereas in normal animals some carbohydrate is spared and more fat and protein are oxidized. These facts alone would justify the expectation that the blood sugar would fall to lower levels and that shock would be more easily induced in hypophysectomized animals receiving insulin. Kater (1936) reported new experiments on the insulin-sensitivity of hypophysectomized rats. Whereas

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[17] According to Di Benedetto and Di Benedetto (1935), hyperglycemia caused by ether is less in hypophysectomized dogs than in control aimals. However, this would be expected if carbohydrate reserves were low as a result of hypophysectomy. Hyperglycemia caused by morphine (30 mg. per kg.) appeared not to be affected.

after the injection of 1–5 (?) units of insulin into normal fast-ing rats, there appeared to be no other change except a fall in the concentration of sugar in the blood from 90 mg. per cent to 60–70 mg. per cent, the injection of 0.05 unit into fasting hypophysectomized rats depressed the level of the blood sugar to 30–40 mg. per cent, with which were asso-ciated myasthenia, rapid, shallow respiration, and coma often with convulsions. The injection of 1 cc. of 20 per cent glucose 15 minutes after the administration of insulin maintained the level of the blood sugar above normal; the rats appeared normal and did not lapse into coma—yet they usually died within about 5 hours. Smith and others (1936) tested the insulin-sensitivity of normal, partially hypophysectomized, and completely hypophysectomized monkeys which first underwent a fast of 16 hours. Thirty minutes after the in-jection of 0.06 unit of insulin per kilogram body-weight, the following changes were observed in the concentration of sugar in the blood of the heart (the figures refer to milligrams per cent; the pre-injection concentration is given first): nor-mal, 115 then 99; partially hypophysectomized, 78 then 66; completely hypophysectomized, 57 then 37. According to Crandall and Cherry (1937), who performed their experi-ments in dogs, either hypophysectomy or denervation of the adrenals—i.e., excision of one adrenal and splanchnotomy on the other side—prevents an increased liberation of glucose from the liver after the injection of insulin. The authors secured blood from the hepatic and portal veins and arterial blood without recourse to anesthesia.

The effect of diet on the response of normal and hypophy-sectomized dogs to insulin was studied by Heinbecker, Somogyi, and Weichselbaum (1937). In operated, but not in normal, dogs the response to insulin was uniformly better if the animals were fed a high-carbohydrate, low-fat diet in comparison with a diet low in carbohydrate and high in fat. On the other hand, Himsworth and Scott found that normal rabbits, on a diet low in carbohydrate, exhibited a disturbed

sugar-tolerance and a diminished sensitivity toward insulin. Diet was without effect in hypophysectomized rabbits which, irrespective of food high or low in carbohydrate, were found to possess a high sugar-tolerance and an increased insulin-sensitivity. However, anterior pituitary extract altered the response of hypophysectomized rabbits to a high-carbohydrate diet, so that it resembled that of normal animals on a low-carbohydrate diet. Cope (1937) was interested in the effect of hypophysectomy on the rabbit's ability to store glycogen in the liver. There seemed to be no interference with this process after the intravenous injection of glucose into fasting animals. However, unlike normal animals receiving no food for 48 hours, hypophysectomized rabbits stored no glycogen in the liver after the injection either of insulin or of epinephrine. After the intravenous injection of lactate, less glycogen was stored by hypophysectomized rabbits than by normal rabbits.

The interrelationship of the pars glandularis and pancreas as revealed by extirpation experiments.[18]—It is well known that Houssay and Biasotti first demonstrated that the course of diabetes mellitus due to pancreatectomy is greatly ameliorated by the removal of the pars glandularis. This observation has been confirmed by a number of investigators who have added new data on the manner in which hypophy-

[18] According to Krichesky (1936), the volume of islet tissue in the pancreas of the rat increases after hypophysectomy. The increase in the volume of islet tissue perhaps was less (in terms of body-weight), if hypophysectomized rats were given injections of anterior pituitary extract. Hypophysectomy was performed 30–60 days before observations were made.

Fichera and Aldoni (1937) studied the pituitary body of depancreatized cats. The pituitary was hypertrophied (20.80 mg. per kg. body-weight compared with 9.69 mg. per kg. body-weight in normal cats). Histological changes were believed to be a marked reduction or even a disappearance of oxyphils and a pronounced increase of the percentage of reserve cells.

The observations of Jacobs and Colwell (1936) are believed to have a bearing on the subject matter of this chapter. These authors infused glucose solution intravenously into non-anesthetized dogs until death occurred as a result of a non-ketogenic acidosis. There was congestion of all the tissues; however, specific, marked hemorrhage and evidences of destruction occurred in the pars glandularis and pancreas.

sectomy modifies pancreatic diabetes. So far as the toad is concerned, Slome (1936) confirmed in another species, *Xenopus laevis*, observations of Houssay and Biasotti who used *Bufo arenarum*. If hypophysectomy be performed first and the pancreas be removed later, the concentration of sugar in the blood of *Xenopus* does not rise above about 40 mg. per cent about 12 hours after the second operation, whereas after pancreatectomy alone it reaches a level of about 230 mg. per cent under similar conditions.[19]

All the other observations were made for the purpose of studying different aspects of metabolism in hypophysecto-mized-depancreatized dogs ("Houssay dogs").[20] The metab-olism of isolated tissues of hypophysectomized-depancrea-tized dogs was studied by Shorr, Richardson, and Sweet (1936) and by Fazekas, Campbell, and Himwich (1937). Ac-cording to Shorr and his colleagues, the metabolism of excised skeletal muscle of doubly operated dogs is like that of normal dogs rather than that of depancreatized dogs, e.g., in capac-ity to utilize added lactate. On the other hand, Fazekas, Campbell, and Himwich concluded that the metabolism of isolated renal tissue of hypophysectomized-depancreatized dogs resembles that of depancreatized dogs, because oxida-tion of lactate but not of glucose takes place.

The experiments of Chambers, Sweet, and Chandler (1937) led them to conclude that relatively little carbohydrate can be oxidized by hypophysectomized-depancreatized dogs. If such dogs were on a diet of meat and carbohydrate, the post-absorptive respiratory quotient was only 0.76. The injection of 50 gm. of glucose daily might or might not elevate the respiratory quotient (+0.05); however 20–80 per cent of the glucose administered appeared in the urine. Carbohydrate-

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[19] Slome found that the level of the blood sugar of fasting normal toads was 35 mg. per cent in animals on a black background, and 26 mg. per cent in animals on a white background.

[20] Képinov (1936) reported that the blood of depancreatized dogs contains a sub-stance producing hyperglycemia but that this substance cannot be detected in the blood if hypophysectomy has also been performed.

balance studies indicated that doubly operated dogs might oxidize as much as 16 gm. of glucose per day. Despite the absence of insulin, hypophysectomized-depancreatized dogs can deposit glycogen in the liver—even in excess of 2 per cent (Chaikoff, Gibbs, Holtom, and Reichert, 1936). These authors also concluded that insulin is essential for the survival of the doubly operated dog but that survival is long if the animal is in an excellent nutritional condition at the time of operation. Chaikoff and his colleagues observed in hypophysectomized-depancreatized dogs all the changes characteristic of pancreatic diabetes, including ketonuria. However, Soskin and others (1935) denied that ketonuria can be detected in such animals.

Interrelationships of the pars glandularis and other glands of internal secretion in affecting carbohydrate metabolism.[21] 1. *The adrenals.*—Problems which have interested investigators in this complex field are illustrated by experiments which Houssay and Biasotti undertook in the toad, *Bufo arenarum.* They relied on quantitative determinations of the blood sugar to measure changes in carbohydrate metabolism. Some fall in the concentration of sugar in the blood appeared after the destruction of all adrenal tissue. Diabetes caused by pancreatectomy was less pronounced, in terms of the level of blood sugar, if either hypophysectomy or adrenalectomy also was performed. In either case, the administration of anterior pituitary but not of adrenal cortical extract caused a further elevation of the level of the blood sugar. The findings were similar if all three structures were removed. The authors suggest the possibility that adrenalectomy may favorably influence the course of diabetes because it lessens the

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[21] It appears that for purposes of discussion there is still too little experimental basis for understanding the manner in which the central nervous system—especially the hypothalamus—affects carbohydrate metabolism, as this is related to the functional activity of the anterior pituitary, the adrenal medulla, and the pancreas. References to recent work in this field are the following: Davis, Cleveland, and Ingram (1935); Dawson and Milne (1935); Houssay (1935); Cleveland and Davis (1936); Ingram and Barris (1936); Lucke (1937).

secretion of the anterior pituitary hormone affecting carbo-
hydrate metabolism.

It is still the belief of Lucke (Lucke, 1936; Lucke and
Kröger, 1936) that the diabetogenic effects of anterior pitui-
tary extract are due ultimately to an action on the adrenal
glands—presumably because unusual amounts of epinephrine
are liberated. This view appears to be untenable, because
extract of the pars glandularis causes typical diabetogenic
effects, including, of course, an elevation of the blood sugar
after removal of all adrenal medullary tissue or bilateral
splanchnotomy (Houssay and Leloir, 1935). However, Hous-
say and Leloir do agree that an immediate temporary rise
in the concentration of sugar in the blood due to the injec-
tion of anterior pituitary extract requires the presence of
adrenal tissue.[22]

Confusion is the chief result of considering reports on the
effects of adrenal cortical extract or of extracts of the anterior
pituitary with cortical-stimulating effects. Anselmino, Hoff-
mann, and Rhoden (1936) concluded that adrenal cortical
extract prevented the loss of hepatic glycogen which other-
wise occurred after the injection of an anterior pituitary ex-
tract into rats. Corey's experiments (1937), likewise in rats,
were performed under different conditions. Adrenal cortical
extract caused hyperglycemia in non-fasted hypophysecto-
mized rats and in normal and hypophysectomized rats fasted
for 48 hours.[23] In the latter group there was no apparent
effect on the glycogen of the liver or muscle; however, the
concentrations of glycogen before injection are not given

[22] Képinov (1936) concluded that the liberation of epinephrine from the adrenal
in response to the injection of insulin is not disturbed by hypophysectomy in the
dog. The liberated epinephrine, however, affected the level of blood sugar much less.
The same author (1937) also believed that anterior pituitary extract or extract of
liver or muscle restores epinephrine glycogenolysis in the liver of the frog after a long
perfusion. An obvious objection to this conclusion is the author's failure to estimate
the lactic acid, glucose, or glycogen in his extracts, although extracts of liver or
muscle of hypophysectomized animals were said not to contain the necessary sub-
stance.

[23] The extracts did not alter the blood pressure of cats anesthetized by "Amytal."

but presumably were low. The observations of Bennett (1937) are difficult to evaluate. An extract of the anterior pituitary causing stimulation of the adrenal cortex was found to prevent a fall in the concentration of glycogen of muscle of hypophysectomized rats, whereas it did not affect hepatic glycogen or blood sugar. However, the effect was not attributed to adrenal cortical stimulating hormone. Treatment for longer periods (10–24 days) did cause an elevation both of the level of glucose in the blood and of the concentration of hepatic glycogen. The effects of repeated injections of the extract on the glucose of the blood and on the glycogen of the liver did not appear in "demedullated," hypophysectomized rats; but the author attributed this finding to cortical deficiency rather than to loss of medullary tissue.

Both the pituitary body and the adrenal glands have been removed from rats by Corey and Britton (1937) and by Samuels, Schott, and Ball (1937). Corey and Britton did not fast their rats and found that doubly operated animals, in comparison with hypophysectomized animals, were unable to maintain the levels of blood sugar (64 mg. per cent compared with 121 mg. per cent), muscle glycogen (0.24 per cent compared with 0.43 per cent), or hepatic glycogen (0.23 per cent compared with 0.94 per cent). According to Samuels and his colleagues, the double operation did not affect glucose tolerance (in comparison with the effect of hypophysectomy alone) but, not remarkably, did hasten death when fasting was instituted. Neither group of authors was in a position to state the relative importance of the cortex and medulla.

Long and Lukens[24] have published further work on the amelioration of pancreatic diabetes by adrenalectomy both in cats and in dogs. The effects resemble those of hypophysectomy in depancreatized animals to such an extent that it is possible to raise the question of whether or not marked lower-

[24] Long (1935), Long and Lukens (1936), Long (1937), and Long, Lukens, and Dohan (1937).

ing of adrenal function as a result of hypophysectomy accounts for the amelioration due to the latter operation. (Another possibility suggested by Long and Lukens is that adrenalectomy suppresses the secretion of diabetogenic hormone by the pars glandularis.) Insufficiency of epinephrine appeared not to be responsible for the prolonged survival of depancreatized-adrenalectomized cats. On the other hand, adequate doses of adrenal cortical extract or of Kendall's crystalline compound B prevent or restore, at least in rats, the marked loss of the glycogen of liver or muscle and the fall in the level of the blood glucose of fasting hypophysectomized animals (Long and Katzin, 1938).

It is, of course, important that there be agreement as to the action or lack of action of anterior pituitary extract after complete adrenalectomy. Houssay and Leloir (1935) concluded that extract can cause a definite increase in the concentration of sugar in the blood of bilaterally adrenalectomized dogs. On the other hand, the more extensive experiments of Long and his associates in the cat and rat indicate that, in the absence of adrenal cortical tissue, glycosuria or an increase of glycosuria does not follow the injection of a potent extract.[25]

2. *The effects of oestrogens.*—Evidence that the injection of large doses of oestrogen prolongs the survival period and ameliorates the symptoms of pancreatic diabetes in the dog and monkey was offered several years ago. Recently, Nelson and Overholser (1936) published further details of their experiments in monkeys and concluded that secretion of the diabetogenic hormone by the pituitary is depressed, with consequent improvement of the symptoms appearing after pancreatectomy, if oestrogen in doses such as 300 rat-units of oestrone be injected daily. Unfortunately, their observations could not be confirmed by Collip, Selye, and Neufeld (1937), who concluded that as much as 1 mg. of oestrin (oestrone?)

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[25] See also Anselmino and Hoffmann (1936) and Russell (1936).

daily affected neither the hyperglycemia nor the glycosuria due to pancreatectomy. Depancreatized monkeys survived even several months without insulin and irrespective of oestrin treatment. The depancreatized monkey resembled the dog or cat after removal of the pancreas and adrenals or of the pancreas and hypophysis.

The effects of extracts of the pars glandularis on the metabolism of carbohydrates.—Young's experiments in dogs (1937)
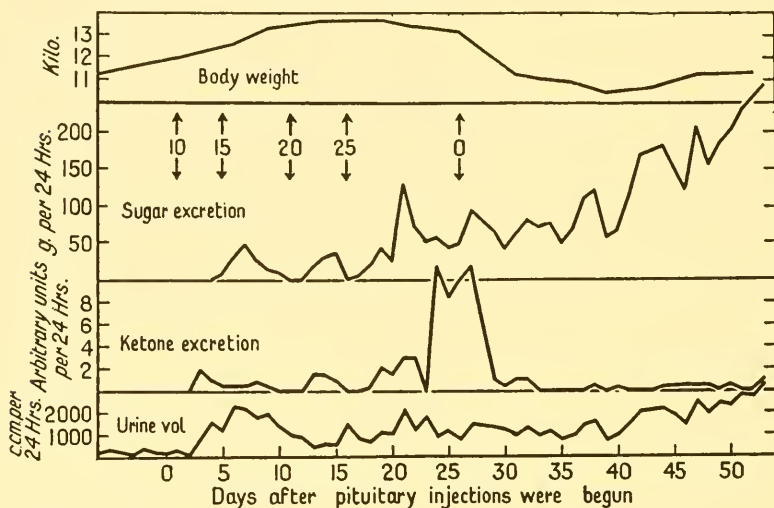
Fig. 24.—Diagram illustrating the production of a condition resembling diabetes mellitus by repeated injections of anterior pituitary into a dog. The numerals between arrows refer to the grams of fresh anterior pituitary of the ox used to prepare the extract injected daily until the next larger amount was used. Injections were stopped on the twenty-sixth day. (From Young, Lancet, **233,** 372–74 [1937].)

indicate that anterior pituitary extract can be truly diabetogenic. Figures 24 and 25 are reproduced from his report. After repeated injections of anterior pituitary extract were stopped, a permanent diabetes mellitus appeared in 2 dogs. However, the animals remained vigorous without the administration of insulin, and in one there was no loss of weight. If insulin was injected to prevent almost entirely the excretion of glucose, it appeared that more was required (4.4 units

per kg. body-weight per day) than in the depancreatized dog. However, Young emphasizes that this is only his impression. Among other general observations are those of Etcheverry (1937) and Foglia and others (1937). Etcheverry concluded that bilateral supra-diaphragmatic vagotomy with or without removal of the abdominal sympathetics does not modify the course of diabetes caused either by pancreatec-
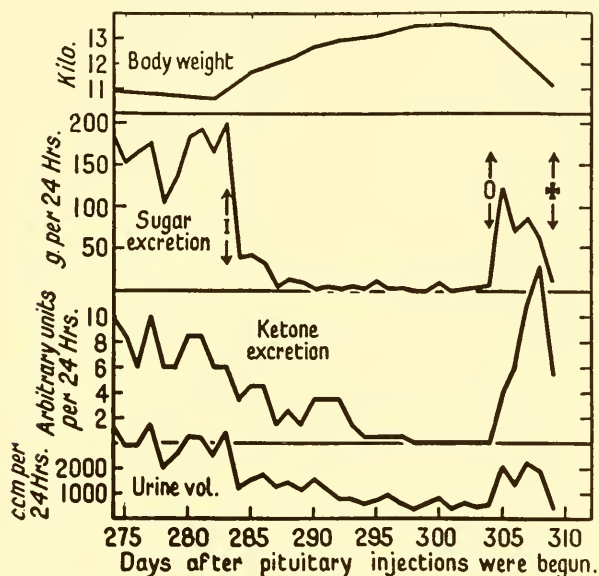
FIG. 25.—Continuation of Figure 24 after a long interval not shown in the diagrams. The daily injection of 60 units of insulin was begun at the first arrow and stopped at the second arrow. Death occurred on day 309. (From Young, Lancet, **233**, 372–74 [1937].)

tomy or by the injection of anterior pituitary extract. Foglia and others injected crude anterior pituitary extract into dogs with diabetes following pancreatectomy. The extract shortened survival time, increased the formation of acetone bodies and the deposition of lipoids in the liver, and antagonized the action of insulin.

The effects of anterior pituitary extract in experiments of short duration were observed in normal and hypophysecto-

mized rats by Fisher, Russell, and Cori (1936) and Russell (1936). To some groups of animals glucose was fed after fasting; the percentage which underwent oxidation was reduced. The respiratory quotient of fasted, hypophysectomized rats receiving injections tended to be lower, i.e., some carbohydrate was spared as is the case when a normal animal fasts. Also, less muscle glycogen disappeared. Russell concluded that the normal rat can deposit much more carbohydrate than the hypophysectomized animal, if anterior pituitary extract be injected after a fast but before the administration of glucose. These observations were extended by Meyer, Wade, and Cori (1937) who used normal rats. The animals were fasted 24 hours, after which they received anterior pituitary extract intraperitoneally. A short time later glucose was fed. The extract produced two principal effects: (1) the amount of carbohydrate oxidized was markedly reduced (following the injection of active extract, the respiratory quotient was 0.77, whereas after inactivated extract it was 0.88), and (2) the carbohydrate spared appeared to be distributed among the liver, striated muscle, and blood and tissue fluids. More than two-thirds was stored in the liver and striated muscle. Bennett (1937) found that, for a short time only, a crude anterior pituitary extract will restore the muscle glycogen to a normal level in hypophysectomized rats. He could not demonstrate "antihormone" in the blood of animals which received much less benefit from repeated injections. An increase in the deposition of glycogen in the liver and probably in striated muscle was demonstrated by Young (1937), who injected anterior pituitary extract into fasting mice and rabbits. He suggests that gluconeogenesis from fat (glycerol?) may be an important part of the effect (rather than a depression of carbohydrate oxidation) or that another principle is responsible for glycogen deposition.

"Pancreatropic" effects of extracts of the pars glandularis.— Several years ago Anselmino and Hoffmann published their first reports on the "pancreatropic" hormone of the pars

glandularis. Extracts of the anterior pituitary were found to cause hypertrophy and hyperemia of the islet tissue of the pancreas of the rat. New formation of islet tissue was also reported. Changes in the level of the blood sugar or hepatic glycogen were found to conform to the interpretation that the extract also promoted the secretion of insulin.

So far as the histological change is concerned, confirmatory reports have been published by the authors themselves, by Picinelli (1936), Chrzanowski and Grzycki (1937), and Roussy and Mosinger (1937). Roussy and Mosinger believed that the effect is associated with suitable contact with neuroganglionic tissue (*neurocrinie pancréatique*). On the other hand, despite efforts to duplicate exactly the experiments of Anselmino and Hoffmann, neither Elmer, Giedosz, and Scheps (1937) nor Santo (1938) could offer confirmatory observations. The obvious importance of an effort to evaluate "pancreatropic" effects quantitatively has been neglected by all authors except Richardson and Young (1937). These authors demonstrated that a saline extract of fresh anterior pituitary of the ox can cause, after daily injection for 2–3 weeks, an increase in the absolute amount of islet tissue as well as a doubling of the ratio of islet tissue to acinar tissue. However, in another strain of rats, receiving no treatment, the ratio was found to be just as high.

There appeared to be little or no effect of the extract of Richardson and Young on the blood-sugar level of their rats. Elmer and his colleagues (1937) likewise could demonstrate no effect with extracts made according to the directions of Anselmino and Hoffmann. Positive results were obtained by Zunz and La Barre (1935). Pancreatropic extract furnished by Anselmino and Hoffmann was injected intravenously into dogs with the pancreatic vein anastomosed with a jugular vein of a second animal which, preferably, was prevented from liberating epinephrine. The injection of the extract caused a lowering of the level of the blood sugar in the second

animal. No noteworthy effect on the thyroid or adrenals (epinephrine-liberation) could be detected.

Anselmino and Hoffmann (1936) injected pancreatropic extract into anesthetized dogs and concluded that the drop in blood sugar produced was increased if the adrenals were removed. These authors also detected the principle in serum and in urine of normal and diabetic individuals and of pregnant women (see also Picinelli, 1936).

The effects of hypophysectomy and of the injection of alkaline anterior pituitary extract (ox) were investigated in adult male newts (*Triturus viridescens*) by Adams and Ward (1936) and appear to be different from those in mammals. For example, the liver was found to weigh more in hypophysectomized newts than in normal animals. After hypophysectomy the liver by histological examination appeared to contain more fat. The authors also investigated the weight, number of islets, and cytology of the islets of the pancreas as well as the concentration of glycogen in the liver by a method of doubtful quantitative value. Although the pancreas was smaller after hypophysectomy, yet it was found to contain an increased number of islets. The reader is referred to their report for a detailed description of their results.

Observations on the effects of serum, cerebrospinal fluid, or urine on the metabolism of carbohydrates.—The observations to which reference is made in the heading of this paragraph are commonly interpreted by the authors as evidence that anterior pituitary hormones affecting carbohydrate metabolism have been identified. This view, of course, may be entirely incorrect. Harrow and others (1936) extracted from the urine of normal young men a substance which causes a marked hyperglycemia in rabbits. Elmer, Giedosz, and Scheps (1937) reported that the serum of a patient with acromegaly produced a similar effect after injection into the rabbit. According to De Wesselow and Griffiths (1936), if the serum of aged individuals with glycosuria be injected

subcutaneously into rabbits, there is definitely less hypo-glycemia produced by a subsequent dose of insulin. This finding suggested that diabetes in the aged may be the result of a relative excess of diabetogenic hormone in the body fluids, because the serum of normal individuals or of young people with diabetes produced almost no antagonism of in-sulin.[26]

Anselmino and Hoffmann (1936), Anselmino and Rhoden (1936), and Anselmino (1937) detected "carbohydrate-metabolism hormone" of the anterior pituitary by the de-crease of hepatic glycogen following administration to rats. In terms of such an effect, the substance has been detected in the serum and urine of young persons with severe diabetes and in the serum of normal individuals or dogs after the ad-ministration of 125–150 gm. of glucose by mouth. The latter change is said not to occur if fat also is fed or if large doses of insulin are given.[27] Anselmino and Hoffmann have not defined in terms of accurate experiments how "carbohydrate-metabolism hormone" is related to the diabetogenic hormone of the majority of authors (see also the report of Anselmino and Hoffmann as published in 1935). Future work must de-cide whether or not "carbohydrate-metabolism hormone" really exists. This is doubted by Singer and Taubenhaus (1937). Diabetes mellitus in relation to "carbohydrate-metabolism" and "fat-metabolism" hormones is discussed by Anselmino and Hoffmann (1935–36) and Effkemann (1936).

In general, diabetogenic extracts of the anterior pituitary do not readily produce changes which can be attributed to antihormone-formation. Although the effects of an extract

[26] Hahndel (1935) stated that the cerebrospinal fluid of normal men, if injected intravenously into rabbits, does not affect the level of the blood sugar. However, if insulin be injected first, the cerebrospinal fluid then causes hyper-glycemia which the author attributes to contra-insulin hormone liberated into the cerebrospinal fluid.

[27] The serum of cattle suffering from "paresis puerperalis"—vegetative endo-carditis with an associated disturbance of mineral metabolism—is reported to pro-duce a decrease of the concentration of liver glycogen in rats without affecting the blood-sugar level (Seekles, 1937).

may appear to diminish progressively, the serum of such animals is reported not to antagonize the hormone's effects in fresh animals (particularly see Young, 1937).

According to Lee and Ayres (1936), hypophysectomized rats lose less "fat," i.e., substances extracted by ether, than normal rats when both groups are fed identical amounts of the same diet. The results of Reiss, Epstein, and Gothe (1937) were variable. A few weeks after hypophysectomy the total fat of the body appeared to have fallen to about 40 per cent of the normal value, to which it returned several weeks later (8 weeks after operation). On the basis of other experiments the authors suggest that adrenal cortical stimulating hormone is of great importance in facilitating the deposition of fat and that this action ultimately depends upon the liberation of adrenal cortical hormone. The administration to man or the dog either of adrenal cortical extract or of pituitary extract causing cortical stimulation was followed by a fall of 25 per cent or less in the concentration of fat in the blood because, according to the authors' interpretation, more fat is deposited in the tissues. In the dog, Chaikoff and his colleagues (1936) found that long after hypophysectomy all the lipoids[29] of the blood may be present in normal concentrations; in about one-third of the animals, however, the lipoids of the blood were present in higher concentrations than were ever encountered in normal animals.

A number of reports are concerned with the behavior of the fat of the liver in relation to the anterior pituitary. In the terminology of Benoit (1937) the "hepatotropic function" of the pituitary is increased in the duck after thyroid-

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[28] Oestreicher (1936) reported that the oxygen-consumption of isolated fatty tissue of the rat (white subcutaneous fat or testicular fat body) is increased by the addition of "thyrotropic hormone" or "fat-metabolism hormone."

[29] Total fatty acids, phosphatide, and free and ester cholesterol.

ectomy; in other words, the removal of the thyroid is fol-
lowed by enlargement of the liver. The experimentally en-
larged liver contains about twice as high a concentration of
lipoids (10.4 per cent) as the normal liver (5.1 per cent), but
if, in addition to thyroidectomy, anterior pituitary extract
be injected into the duck, there is further hypertrophy and
the concentration of lipoid rises to 38.6 per cent (Benoit,
1936). The observations of Best and Campbell (1936) were
made in rats. Large doses of anterior pituitary extract were
followed by the deposition of large amounts of fat (total fatty
acids together with unsaponifiable material) in the liver. As-
sociated changes in fasting rats were a decrease in the fat of
other parts of the body and an increased excretion of acetone
bodies. The accumulation of fat in the liver as a result of the
injection of anterior pituitary extract is prevented by adren-
alectomy but not by demedullation of the adrenals (Fry,
1937). Likewise, MacKay and Barnes (1937) showed that
adrenalectomy prevents the deposition of fat in the liver,
caused either by anterior pituitary extract or by fasting.

Pancreatectomy is ordinarily followed by an accumulation
of lipoids in the liver of animals such as the dog. This change
is not prevented if hypophysectomy also is performed (Chai-
koff and others, 1936).

The relation of what Anselmino and Hoffmann term the
"fat-metabolism hormone" to the accumulation of lipoids in
the liver is not clear. Pituitary extract may cause, under
proper experimental conditions, an accumulation of acetone
bodies in the blood and an increased excretion of the bodies
in the urine. An extract with such effects is what Anselmino
and Hoffmann have called the "fat-metabolism hormone."
Its other effects come up for discussion shortly. Although
Anselmino, Hoffmann, and Rhoden (1936) state that extract
with the previously described properties is identical with the
active substance present in the extracts of Best and Camp-
bell and causes an increase of about 50 per cent in the con-
centration of ether-soluble substances in the liver dried at

60° C., their earlier report (Anselmino, Effkemann, and Hoffmann, 1935) emphasized that (1) the consistent effect of the extract is an unsaturation of fatty acids of the liver and (2) the concentration of total fatty acids in the liver falls or rises depending upon the presence of high or low initial levels.[30]

It must be remembered that, if the concentration of acetone bodies in the blood increases or if the urinary excretion of these bodies becomes markedly elevated after the injection of anterior pituitary extract, these facts do not justify naming the causative substance "fat-metabolism hormone." The experimental data indicate that its action depends upon the presence of intact adrenal tissue. Dingemanse (1936) is not convinced that a ketogenic hormone exists and found (1) that only an occasional extract raises the level of acetone bodies in the blood of the rat (but not the rabbit), (2) its detection is difficult because of the effect of fasting, time of day, etc., and (3) the ratio of β hydroxybutyric acid to acetoacetic acid and acetone is the same, whether ketogenesis is caused by fasting or by extract.

Mirsky (1936) takes the position that inasmuch as ketogenesis cannot occur in the absence of the liver, a ketogenic effect depends upon the utilization of non-carbohydrate foods in the absence of ample carbohydrate available for oxidation by the cells of the liver. He prevented the ketogenic action of anterior pituitary extract in rabbits fasted for 24 hours by the injection of insulin (1.3–3 units per kg. body-weight) or ergotamine tartrate (2 mg. per kg. body-weight). Both of these substances were considered to prevent glycogenolysis, thus acting as ketolytic agents. Anselmino and Hoffmann (1936) concluded that insulin inhibits the liberation of a ketogenic hormone occurring otherwise as a result of feeding butter. The authors used dogs.

[30] The same authors (1935) stated that "carbohydrate-metabolism hormone" causes an effect the opposite of (1) and also brings about a fall in the concentration of total fatty acids.

There appears to be little doubt that the ketogenic effect of anterior pituitary extract, as determined by ketonuria in the rat, is prevented by the removal of the adrenal glands (Fry, 1937; Houssay and Rietti, 1937; MacKay and Barnes, 1937). The acetoacetic acid of blood was determined by Houssay and Rietti, whereas the other investigators estimated the acetone bodies of urine. Cortical tissue alone seemed to be necessary for a ketogenic action, inasmuch as the latter is not affected by demedullation (Fry). Houssay and Rietti stated that the administration of adrenal cortical extract restores the ketogenic action of anterior pituitary extract in adrenalectomized rats, whereas this is not accomplished by means of salt therapy.[31]

According to Fry (1937), the ketogenic effects of anterior pituitary extract can be observed in the rat even 7 weeks after thyroidectomy. However, Best and Campbell (1936), who performed their experiments in rabbits, found that as hypothyroidism became more pronounced (e.g., 4–6 weeks postoperatively) no ketogenic effect could be produced unless thyroid extract was administered.

Anselmino and Hoffmann (1936) discuss the extraction of ketogenic principle from the anterior pituitary and from blood and urine. Its detection in the blood and urine of diabetic individuals has been reported (Anselmino and Hoff-

[31] Mirsky (1938) suggested that adrenalectomy in the rat does not affect ketogenesis caused by anterior pituitary extract as measured by the acetone bodies of the blood, but that the operation does raise the threshold of renal excretion of acetone bodies. Thus, authors investigating only ketonuria would erroneously conclude that the operation prevented the ketogenic action of extract. However, Houssay and Rietti studied the acetoacetic acid of blood and found that adrenalectomy largely prevented (or even reversed) the ketogenic effect of extract 6–14 days after operation. Earlier than 6 days after adrenalectomy, when Mirsky made his observations (48 hours after operation), Houssay and Rietti found that the ketogenic action of extract was unimpaired. If the method of estimating acetoacetic acid used by Houssay and Rietti be considered accurate, their extract produced an adequate ketosis, inasmuch as acetoacetic acid probably represents less than 20 per cent of the total acetone bodies.

Anselmino, Hoffmann, and Rhoden (1936) concluded that adrenal cortical extract fully antagonizes the ketogenic action of anterior pituitary extract.

mann, 1936; Taubenhaus, 1936).[32] If a ketogenic pituitary extract be injected repeatedly, the animal becomes refractory to this effect (Bennett, 1937).

Teilum (1937) attributes to the pituitary the hypercholesterolemia which he observed invariably in gonadectomized persons or patients with hypogonadism. He offers no satisfactory evidence for this interpretation. If we accept the data of Cioglia and Tore (1936), gonadectomy is followed by hypocholesterolemia (rabbit). These authors observed hypercholesterolemia after the administration of prolan or pituitary gonadotropic hormone.

THE METABOLISM OF PROTEIN AND SOME NON-PROTEIN NITROGENOUS COMPOUNDS IN RELATION TO THE ANTERIOR PITUITARY

The metabolism of protein in relation to the pituitary body.— In addition to references in other chapters, there remain a few general reports on the metabolism of protein. Gaebler and Price (1937) studied the action of single large doses of anterior pituitary extract (with growth-promoting properties) on the metabolism of protein in dogs. The authors found that a fall in the rate of excretion of N, S, and phosphate was associated with a rise in weight. At the same time the ratio of N to S increased and more N was retained. All these changes are similar to those occurring when synthesis of protein is in progress and suggest that the extract had, in fact, brought about an increased rate of protein synthesis.[33]

[32] The obesity of a patient with Cushing's syndrome was considered by Freyberg and Newburgh (1936) not to be caused by any unusual metabolic derangement, because loss of weight due to undernutrition took place exactly as in normal persons.

[33] See also the report of Paschkis and Schwoner (1937), who investigated the action of commercial anterior pituitary extracts on the level of the amino acids in the blood of patients who had been given gelatine by mouth.

Binet, Képinov, and Weller (1935) published determinations of reduced and total glutathione in the liver, thyroid, and testis of normal and hypophysectomized dogs. Hypophysial deficiency was found to be accompanied by reductions in the concentration of glutathione in all three tissues; the most marked reduction occurred in the thyroid, the least in the testis.

Perla and Sandberg (1936) observed that the excretion of N in the urine is increased by 100 per cent during the first few weeks after hypophysectomy and remains elevated for weeks later. The observations of Yokoyama (1935) indicated that, several weeks after hypophysectomy, the dog excretes considerably less total N, uric acid, and urea. Slighter but similar changes in the behavior of allantoin, ammonia, and creatinine were also reported.

The metabolism of creatine and creatinine in relation to the anterior pituitary.—The excretion of nitrogen and creatinine are about the same in normal and hypophysectomized rats, provided that the diet contains sufficient protein. However, if the diet is free from nitrogen, less of both constituents is excreted by hypophysectomized animals. Braier and Morea (1935) interpret these findings as further evidence that endogenous protein metabolism is reduced as a result of hypophysectomy.

The concentration of creatine in the hamstring muscle of the toad (*Xenopus laevis*) falls about 15 per cent 18–22 weeks after the removal of the pars glandularis or the whole pituitary. The opposite effect is produced by the injection of anterior pituitary extract—the concentration of creatine may increase about 30 per cent 3–5 weeks after injections are started in normal toads. These observations were reported by Shapiro and Zwarenstein (1936), who believed that the effect is mediated through another gland.[34] Nitzescu and Gontzea (1937) concluded that the anterior pituitary extract "Antuitrin G," although without effect in normal individuals, increases the creatinuria of patients classified as suffering from infantilism, dwarfism, and dystrophia adiposogenitalis. The extract also lessened the tolerance for creatine

[34] The secretions of the gonads are of great importance in the metabolism of creatine; e.g., Kun and Peczenik (1936) recently concluded that, at least in the rat, creatinuria appears if there is testicular deficiency and disappears after the injection of male hormone, whereas spayed females excrete no creatine in the urine unless an oestrogen be injected. The male and female hormones, therefore, appeared to affect creatine-metabolism in opposite directions.

and antagonized the effect of male hormone ("Erugon") on creatine-excretion.

According to Perla and Sandberg (1936) creatinuria transiently appears in male but not in female rats after hypophysectomy.

The pituitary body and the metabolism of minerals (*except calcium*).—Gerschman and Marenzi (1935) reported that the injection of large doses of alkaline anterior pituitary extract into hypophysectomized dogs was followed by a diminished concentration of Na and Cl in the blood, whereas the concentration of "CO_2," glucose, Ca, Mg, and inorganic P was elevated following this treatment. Friedgood and McLean (1937), however, could not observe any change in the concentration of serum phosphate of guinea pigs receiving daily injections of alkaline anterior pituitary extract for more than a week. Perla and Sandberg (1936) found that hypophysectomy accelerates the loss of P in the feces (but not in the urine) of rats. Later, a study of the effects of partial or complete hypophysectomy on the metabolism of water, Na, K, Cl, and S was made in rats by Sandberg, Perla, and Holly (1937). The reader is referred to their article for a description of their findings. That the concentration of Mg in blood is greatly affected by anterior pituitary secretion is the belief of Cannavò and Beninato (1935), who extended the work of their laboratory in this aspect of mineral metabolism. The pituitary of rabbits was irradiated by X-rays so that the pars glandularis was severely injured and a cachexia followed by death in 2–3 weeks appeared. The serum-concentration of neither Ca nor inorganic P was clearly affected. About 10 days after irradiation the level of Mg was reduced from the normal level (3.25–4.04 mg. per cent) to a new, lower level (1.83–2.54 mg. per cent). The authors believed that the ex-

cretion of Mg both in the urine and in the feces was reduced in irradiated animals.

According to the interpretation of Brull (1937) the pituitary body is important in the maintenance of the level of inorganic P in the blood, because after hypophysectomy the renal threshold for PO_4 rises. In the dog anesthetized by chloralose, the excretion of PO_4 almost disappears but can be reinstated by the injection of parathyroid hormone, which is believed to act directly on the kidneys. If hypophysectomy is then performed, urine is excreted at an increased rate, but PO_4 almost disappears from the urine, although its concentration in the blood rises from a level of 8.4 mg. per cent to a level of 10.0 mg. per cent.

The pituitary body and the metabolism of calcium. The interrelationship of the pars glandularis and the parathyroid glands.[35]—Some further evidence that parathyroid function is affected by the anterior pituitary has been published. Gerschman and Marenzi (1935) concluded that large doses of alkaline anterior pituitary extract can cause a small elevation (1.9 mg. per cent) of the level of Ca in the blood of dogs and that such an effect still can be produced after hypophysectomy or thyroidectomy but not after thyroparathyroidectomy. However, the authors' data do not include the level of Ca after thyroparathyroidectomy but before injection; after injection the concentration of Ca was 5.02 mg. per cent. The reports of Speransky-Stepanova (1936) (Speranskaia-Stepanowa) were based upon observations in two hypophysectomized dogs. The level of Ca in the serum was not affected by hypophysectomy but promptly fell after subsequent thyroparathyroidectomy which, of course, caused tetany.[36] Both in rats (Friedgood, 1936) and in guinea pigs (Friedgood and

[35] Freyberg and Grant (1936) studied the metabolism of Ca and P in a patient described as suffering from pituitary basophilism. The changes, contrary to what might be expected, were found not to resemble those of hyperparathyroidism (see also the review of Rivoire, 1935).

[36] Tetany was not accompanied by an inhibition of diuresis as in dogs with an intact pituitary.

McLean, 1937) alkaline anterior pituitary extract can cause an elevation of 0.9–2.0 mg. per cent in the concentration of Ca in the serum.

An increased excretion of Ca in the urine following hypophysectomy has been observed in the rat by Perla and Sandberg (1936). The change in absolute terms was slight but represented an increase of several hundred per cent. Perla and Sandberg found that the principal loss of Ca occurred by way of the digestive tract and that fecal loss was increased after hypophysectomy. Teel and Cushing had found that the urinary loss of Ca by the dog is increased after the injection of anterior pituitary extract.

Anselmino, Hoffmann, and Herold, who first described histological signs of a parathyrotropic effect of anterior pituitary extract have investigated the action of an aqueous extract of acetone-desiccated anterior pituitary powder (ox) in various animals (Anselmino, Herold, and Hoffmann, 1936). They stated that macroscopic enlargement could be produced in the rat and rabbit but not in the cat, dog, or guinea pig. In all the species, histological changes appeared—principally hyperplasia of cells resembling the chief cells of the normal parathyroid.

MISCELLANEOUS OBSERVATIONS

Perla (1936) investigated the relationship between the spleen and the anterior pituitary and concluded that the gland is required for the normal maintenance of the spleen.[37] However, it is not possible to state that the anterior pituitary secretes a separate spleen-stimulating principle. Hypophysectomy in rats is followed by splenic atrophy, which regresses considerably if an emulsion of pituitary be injected. Regeneration of a remnant of the spleen after partial splenectomy likewise is prevented by hypophysectomy but takes place as a result of administration of pituitary emulsion. The injection of an emulsion of anterior pituitary of the ox into

[37] See also Friedgood (1936) and earlier reports on the effect of hypophysectomy.

normal rats—or of an alkaline extract of fresh or desiccated gland—can cause a marked hypertrophy of the spleen due chiefly to hyperplasia and hypertrophy of the reticulo-endo-thelial cells of the red pulp. In addition, there is some growth of follicles, but the Kupffer cells are not affected. Hyper-plasia of the reticular cells of the bone marrow likewise oc-curs. Wetzler-Ligeti and Wiesner (1937) measured the effect of anterior pituitary extract on the reticulo-endothelial sys-tem by the rate at which Congo red was removed from the blood after the dye had been injected intravenously. They concluded that anterior pituitary extracts can either favor or interfere with the removal of Congo red from the circulating blood (positive and negative "restropic" effects).

The relation of the pituitary to erythrocyte- (and leu-cocyte-)formation was investigated by Kapran (1935) and Flaks, Himmel, and Zlotnik (1937). Kapran reported on the changes following hypophysectomy in the dog—i.e., di-minished number of erythrocytes, elevated color-index, in-terference with reticulocyte formation, slight leucopenia, and eosinophilia even to 20 per cent; but that these changes were specifically due to hypophysectomy was not shown. On the other hand, McFarlane and McPhail (1937) were unable to detect any change in erythrocyte count or content of hemo-globin in guinea pigs because of the removal of the pituitary. According to Flaks and his colleagues, a thermostable sub-stance can be extracted from the anterior pituitary which di-rectly stimulates the red bone marrow even after adminis-tration by mouth. Reticulocytosis and later polycythemia can be observed in rats receiving the extract.

Keller and D'Amour (1936) occasionally found hemorrhage into and ulceration of the gastrointestinal tract of dogs in which hypophysectomy had been undertaken. However, they were not certain that these pathological changes were not caused by injury of the central nervous system. Belief in the efficacy of heterotransplants of the anterior pituitary was expressed by Kylin (1937), who concluded that they were

of great value in the treatment of Simmonds' disease; he also described the successful transplantation of calf pituitary into the peritoneal cavity of the rabbit.

According to Gagyi (1936), who performed titrations with 2,6 dichlorophenolindophenol, the pars neuralis (contrary to Giroud and Leblond) contains about three times as much ascorbic acid as the pars buccalis in terms of concentration (pars neuralis 7.2 and the pars glandularis–pars intermedia 2.3 mg. per gm). Also he stated that the gland of immature animals, especially females more than males, contains a higher concentration of the vitamin than the gland of adults. The observations were made in guinea pigs. Two other reports refer to constituents of the pituitary. Regnier (1936) found that sulfonal (diethylsulfonmethane) was deposited in the pars glandularis to a greater extent than in any other tissue after the drug had been administered by mouth to a horse (40 gm. to a horse weighing 450 kg.). The tissues containing the highest concentrations of this hypnotic, expressed as milligrams per 100 gm., were: pars glandularis, 750; adrenals, 426; pars posterior, 200; blood, 29.4. The brain contained 7.8 mg. per 100 gm. It is extremely unlikely that the presence of bromine in the pituitary body has any significance. Dixon's recent report (1935) indicated that the pituitary of the normal pig contains about 0.27 mg. of Br per 100 gm. of fresh tissue. As in other organs the ratio of Br to Cl roughly corresponded to what was probably the ratio of these elements in the diet. According to Moruzzi and Guareschi (1936), the fresh pituitary of the ox and of man contains respectively about 1 or about 0.6 mg. of Br per 100 gm.

SUMMARY

The morphological and functional maintenance of the cortex of the adrenal glands depends upon secretion(s) of the pars glandularis. (The medulla of the adrenal gland may have important indirect interrelationships with the anterior pituitary; its direct dependence on the anterior pituitary prob-

ably is slight and unimportant.) Without pituitary secre-
tion either from the intact gland or from administered ex-
tract, the adrenal cortex rapidly diminishes in size and per-
forms its usual functions only imperfectly. The principal
morphological evidences of atrophy are in the outer part of
the thickest layer of the cortex, the zona fasciculata, al-
though the zona glomerulosa also is affected. There is a
striking loss of lipoids. The administration of a suitable an-
terior pituitary extract not only restores the lipoids lost but
may increase their concentration in association with hyper-
trophy and hyperplasia of cortical cells. In this way an ex-
tract may cause cortical enlargement in hypophysectomized
rats, so that the adrenal glands are larger than any ever en-
countered in normal rats receiving no treatment.

The X-zone of the innermost part of the cortex of young
female mice or of castrated males seems also to depend upon
an anterior pituitary hormone for its development (Deanes-
ly).

The physiological interrelationships of the adrenal cortex
and the anterior pituitary are important and numerous; un-
fortunately, however, they have been explored only imper-
fectly. Compensatory adrenal hypertrophy requires adrenal
cortical stimulating hormone. This hormone probably is se-
creted at an increased rate if there is cortical deficiency,
whereas a change in the opposite direction takes place if
abnormally large amounts of adrenal cortical hormone(s) are
present in the body-fluids. Some of the most important cor-
relations appear to affect the metabolism of carbohydrates
and fats and are mentioned in later discussion.

The pars glandularis appears to be the principal division
of the pituitary body important in the metabolism of car-
bohydrates. The substance or substances responsible for par-
ticipation in this important phase of metabolism has been
detected in anterior pituitary extracts which, for the most
part, are quite crude. The isolation of these substances must

be carried much farther before definite statements can be made concerning either their number or their other biological effects (e.g., on the mammary glands or adrenal cortices). However, a number of other methods has been employed to learn how regulation by the anterior pituitary is effected. Carbohydrate metabolism has been studied after hypophysectomy; in such studies, epinephrine or insulin also has been used. The remarkable amelioration of diabetes which follows the removal of the hypophysis from depancreatized animals has received further attention. The most important interrelationships with other glands of internal secretion are those with the pancreas and adrenal glands.

The anterior pituitary appears to be necessary for the absorption of glucose at a normal rate from the digestive tract; however, there is no evidence that a specific hormone, such as that affecting the metabolism of carbohydrate after absorption, alters the process of absorption. The "diabetogenic" hormone of the anterior pituitary probably prevents the prodigal waste of important, but sometimes small, carbohydrate reserves which, for example, are maintained in spite of fasting. An animal isolated from all sources of the hormone (as after hypophysectomy) and dependent upon its own reserves of food, dangerously uses up all available carbohydrate. It is able readily to mobilize the glycogen of both the liver and striated muscle and to oxidize glucose. Perhaps another important metabolic function of anterior pituitary secretion is to facilitate the new formation of carbohydrate from both fat (glycerol) and protein.

The diabetogenic hormone can be viewed as an antagonist of insulin, the internal secretion of the pancreas. There is evidence that this antagonism is indirect and depends upon the support of adequate adrenal function. However, there is not complete agreement that bilateral adrenalectomy prevents the disturbing effects of anterior pituitary extract on carbohydrate metabolism—e.g., hyperglycemia in the dog. On the other hand, the glycosuria which follows the injection of an-

terior pituitary extract into cats or rats is not observed after complete adrenalectomy. Insulin-sensitivity is increased by hypophysectomy, because an important physiological antagonist of insulin—diabetogenic hormone—is no longer available, and carbohydrate reserves both disappear at an abnormally rapid rate and probably are restored from other endogenous sources only with great difficulty. After pancreatectomy, secretion(s) of the anterior pituitary is not antagonized (however indirectly) by insulin and may be regarded as an important contributor to changes which threaten life—e.g., the accumulation of acetone bodies. Anterior pituitary secretion can also be pictured as interfering with the oxidation of glucose which otherwise is facilitated by insulin. If, however, both glands are removed, the important means of regulating carbohydrate metabolism are lost. A unique derangement of metabolism appears and, depending upon conditions such as nutritional state before operation, fasting, diet, etc., the animal resembles sometimes the diabetic animal—e.g., with hyperglycemia and glycosuria—and sometimes the animal with hypophysial deficiency—e.g., with hypoglycemia.

Although the effects of subcutaneously injected epinephrine are less pronounced after hypophysectomy, it is probable that delay in absorption accounts for most of this change, provided that reserves of carbohydrate are adequate. Any diminished effect of epinephrine is observed in respect of all the expected changes—elevation of the level of sugar and lactic acid in the blood, depression of the level of inorganic P, lowering of the concentration of glycogen in muscle, etc.

New observations support the belief that anterior pituitary extract can cause hypertrophy of the islet tissue of the pancreas. The physiological significance of this effect has not been adequately explored.

Any attempt briefly to summarize our knowledge of the relation of the anterior pituitary to carbohydrate metabolism is necessarily confusing, because we know only some phases

of processes of unknown complexity. However, the potential value of what can be learned is immense in its implications not only to physiology but also to clinical medicine.

The metabolism of fat, depending upon conditions, is probably closely interrelated with that of carbohydrates. Since little is known concerning the nature of the substance(s) affecting the metabolism of carbohydrates and fats which can be extracted from or are secreted by the pars glandularis, it is by no means clear whether or not one or more substances is responsible for the effects, or, indeed, whether the effects are due to a hormone to which another name has already been given. Perhaps an anterior pituitary hormone which depresses the rate of catabolism of carbohydrate (and increases the rate of protein anabolism) indirectly necessitates the mobilization and oxidation of an increased proportion of fat, so that ketogenesis is facilitated. The outstanding facts concerning the effects of pituitary extract on the metabolism of fat appear to be (1) large doses of anterior pituitary extract bring about a deposition of fat in the liver which, in fasted animals at least, is enriched at the expense of other tissues and (2) anterior pituitary extract produces ketosis which probably is associated with the changes described under (1). (It is generally believed that acetone bodies are formed in the liver.) It is of great interest that both of these changes are said to be prevented by adrenalectomy, apparently because of the removal of the cortex. This, in turn, suggests that an adrenal cortical stimulating substance is the pituitary secretion affecting the metabolism of fats.

There still is not a sufficiently large body of data to enable one to discuss with any assurance the manner in which the metabolism of proteins is influenced by secretion(s) of the pars glandularis. It appears that hypophysial deficiency probably is accompanied by increased catabolism of proteins of endogenous origin and imperfect utilization of proteins of

exogenous origin, whereas anterior pituitary extract favors protein synthesis.

Additional reports on the interrelationship of the anterior pituitary and the metabolism of minerals have been made. However, there frequently is a lack of agreement. Possible effects of extracts on the metabolism of water are usually neglected. There is evidence that the activity of the parathyroid glands is regulated to some extent by the pars glandularis. This control appears to be slight and is much less effective than that exercised over the adrenals, gonads, or thyroid.

CHAPTER VIII

THE PITUITARY BODY IN RELATION TO THE REGULATION OF THE DISTRIBUTION OF PIGMENT IN CHROMATOPHORES

CELLS containing granules of pigment of various colors may be found in the skin and other tissues of cold-blooded animals. These cells often are of great importance in the adaptation of color to background or in effecting color changes for other purposes—e.g., that associated with the breeding season. The change of color is effected by the movement of the granules of pigment, chromatosomes, in cells which are called chromatophores. These cells commonly are named in accordance with the color of the pigment they contain. Melanophores are so named because they contain melanin-granules for which the term melanosomes will be used. Likewise erythrosomes refer to the granules of red pigment in erythrophores, etc.

The pituitary body is of importance in this aspect of biology because extracts of the pars intermedia (or of the pars glandularis) may bring about a striking dispersion of chromatosomes, especially melanosomes or erythrosomes. The removal of most of the pituitary may be followed by the opposite effect, e.g., a marked concentration of the melanosomes may follow hypophysectomy in the frog. In addition, Hogben and his collaborators have inferred that a hormone of the pars tuberalis is important in certain amphibia in bringing about adaptation to light backgrounds.

The degree to which the position of pigment-granules in chromatophores is regulated by the pituitary body varies greatly in different classes of animals, such as fishes, amphibia, and reptiles. The importance of the gland generally

[244]

is more easily demonstrated in certain amphibia than in animals of other classes.[1]

The importance of the pituitary body in regulating chromato-some dispersion in fishes.—In fishes hypophysectomy often is followed by a marked concentration of the melanosomes (the "melanophore contraction" of some authors). However, the change appears more sluggishly than in amphibia. Most of the successful experiments have been performed in various elasmobranchs. Lundstrom and Bard had shown that the removal of the neuro-intermediate lobe from the dogfish, *Mustelis canis*, is followed by a marked pallor of the skin due to the concentration of the melanosomes in the central part of the melanophores. As a phase of his investigation of the physiology of the chromatophores of various animals, Hogben (1936) studied the effects of hypophysectomy in several elasmobranchs. Figure 26 is reproduced from Hogben's article and illustrates the cutaneous pallor of *Rhina squatina* following hypophysectomy. The adaptation of fishes such as dogfishes (*Scyllium catulus, S. canicula*), the angel shark (*Rhina squatina*), and rays (*Raia maculata, R. brachiura*) to a black background is abolished by hypophysectomy. However, in some species the operation may not be followed by as striking a macroscopic effect as is illus-

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[1] Abramovitz (1936–37) has published several reports extending the observations of Megasŭr and of Carlson on the hormone in the eye-stalks of crustacea. This hormone appears to be responsible for melanosome dispersion in crustacea such as *Callinectes, Libinia, Palaemonetes,* and *Uca.* Extirpation of the eye-stalks of the crab, *Uca,* is followed by paleness of the integument (Megasŭr); if an extract of eye-stalks be injected into such pale crabs, dispersion of the melanosomes occurs and the animal becomes dark (Carlson). Abramovitz found that an extract of the eye-stalks of *Palaemonetes vulgaris* produces effects similar to those of the chromatosome-dispersing hormone of the pituitary. This was shown by the dispersion of the pigment in the melanophores following injection of the extract into light-adapted or hypophysectomized fishes (*Ameiurus nebulosus, Mustelis*), frogs (*Rana pipiens*), or reptiles (*Anolis carolinensis*). The erythrophores and melanophores of the dace (*Chrosomus erythrogaster*) were similarly affected.

The substance responsible for these effects was found to be remarkably stable. It could survive boiling in water or in aqueous solutions of 1 per cent HCl or KOH. It appeared to be soluble in water and in methanol or ethanol—although the extent to which this is true was not accurately described.

trated in Figure 26. As in the dogfish, the loss of the neuro-intermediate lobe is responsible for the failure of the melanosomes to disperse when the background is black. Hogben is of the opinion that adaptation of elasmobranchs to light backgrounds, due to a concentration of the melanosomes, de-

Left   *Right*

Fɪɢ. 26.—The effect of hypophysectomy on the appearance of the adult angel-shark, *Rhina squatina*. *Left:* normal; *right:* hypophysectomized 10 days before. Both kept continuously in black tank. (From Hogben, Proc. Roy. Soc., B, **120**, 142–58 [1936].)

pends upon a secretion from a part of the pars buccalis homologous with the mammalian pars tuberalis. However, adaptation to light backgrounds may be slight, e.g., in *Raia clavata*. Hogben's results support the general belief that the pars intermedia of the pituitary body of animals in which it can be identified morphologically elaborates the secretion

[246]

causing dispersion of the melanosomes.[2] In fishes, as in amphibia, optic stimuli chiefly determine whether or not the secretion will be released.

Likewise in elasmobranch fishes, other authors have demonstrated that hypophysectomy is followed by a cutaneous pallor which persists irrespective of the background. Barry (1937) described a dogfish (*Scylliorhinus canicula*), the cutaneous melanophores of which resembled those of a hypophysectomized fish in respect of the unchanging concentration of the melanosomes and their rapid dispersion after the injection of a pituitary extract. However, his description of the histological appearance of the pituitary body and its related structures is of little assistance in explaining the phenomenon. The removal of the pituitary from *Torpedo marmorata* causes a light coloration of the skin as a result of melanosome concentration (Veil and May, 1937). Vilter (1937) attributed the "melanophore contraction" which appears as a result of hypophysectomy in two rays, *Trigon pastinaca* and *Raia undulata*, to a pronounced tonus of the sympathetic nervous system because ergotamine, which may cause paralysis of sympathetic terminal fibers, brought about a marked dispersion of the melanosomes in either normal or hypophysectomized fishes of these species.[3]

In teleost fishes the role of the pars intermedia in effecting color changes by means of the melanosome-dispersing hormone is less important and often is difficult to evaluate. Veil recently stated (1937) that the removal of the gland from the catfish (*Ameiurus*) is followed by blanching of the skin, which can again be made dark by the administration of fish pituitary or an extract of the mammalian posterior lobe. According to Parker (1935), chromatosome dispersion in *Ameiurus*

[2] Neither the oxytocic nor the vasopressor hormone of the pars neuralis is responsible for melanosome dispersion.

[3] For years, epinephrine has been regarded as a substance causing melanosome concentration. So far as fishes are concerned, it appears that the importance of a sympathetic innervation of the melanophores is greater in teleosts than in elasmobranchs.

is effected both by nervous impulses and by the hormone; however, he regarded the latter as the less important. Parker believed that melanosome concentration is chiefly under the control of the (sympathetic) nervous system in both teleosts and elasmobranchs, whereas in elasmobranchs the dispersion of pigment-granules is due to a hormone of the pituitary. In another teleost, *Fundulus heteroclitus*, both the light and dark phases of pigment distribution appeared to be regulated by nerves (Parker). However, Kleinholz (1935) showed first that the pituitary of *Fundulus* contains melanosome-dispersing hormone as demonstrated by experiments in catfish, frogs, and lizards, and second, that denervated melanophores of *Fundulus* responded in a typical fashion (melanosome dispersion) to extracts of the pituitary of *Fundulus*, of the frog, or of the mammal.[4] Such an effect was never observed in melanophores with a normal innervation. Abramovitz (1937) concluded that the melanosome-dispersing hormone of the pituitary probably is of real significance in the physiology of the melanophores in *Fundulus*, despite the fact that adaptation to light and dark backgrounds ordinarily is not affected by hypophysectomy. Abramovitz found that the operation prevented the complete dispersion of the melanosomes of denervated melanophores, when the fish were placed on a black background.

In other teleost fishes such as *Phoxinus laevis* the distribution of pigment in erythrophores is principally affected by the chromatosome-dispersing hormone of the pars intermedia. Fleischmann and Kann (1937) injected posterior-lobe extract into several species of marine fishes (*Coris julis*, *Crenilabrus pavo*, *Serranus scriba*, and *Tripterygium nasus*) and found that the changes in coloration strongly resembled those appearing in fishes in full "wedding dress." They were unable to detect an effect on the melanophores. Erythro-

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[4] The melanosomes of isolated scales of *Fundulus* generally become concentrated, if the scales are placed in a solution of posterior-lobe extract. Such an observation is of little assistance for purposes of interpretation.

some dispersion in the erythrophores of intact fish or of isolated scales has again been used in recent experiments for purposes of assay.

The regulation of chromatosome dispersion in amphibia.[5]— Especially in anuran amphibia past work has shown that adaptation of the skin's color to dark or black backgrounds chiefly depends upon an internal secretion of the pars intermedia. After the removal of the pars intermedia (or the neuro-intermediate lobe), marked aggregation of the melanosomes takes place, so that animals like the frog remain pale indefinitely, irrespective of the background. Atwell and Holley (1936) found that the pars intermedia may be removed from tadpoles, and yet sufficient tissue of the pars glandularis is spared, so that in such silvery tadpoles complete or partial metamorphosis occurs and normal development of the thyroid, gonads, and adrenals takes place. The authors suggested that the pars intermedia of tadpoles of *Rana sylvatica* can undergo development without contact with nervous tissue.

New studies by Hogben and Slome (1936) support their conclusion that both the white- and black- background responses of the toad, *Xenopus laevis*, depend upon hormones. Their study was limited to the dermal melanophores and indicated that dispersion of the melanosomes is caused by a hormone of the pars intermedia, whereas concentration of the melanosomes is dependent upon an intact pars tuberalis. Their results are summarized in Table 8. Presumably the low sensitivity of the melanophores toward the melanosome-dispersing hormone in animals without a pars intermedia (and pars neuralis) is due to the pars tuberalis, the effects of the secretion of which are no longer antagonized by the normal secretion of the pars intermedia. On the other hand, the great sensitivity of the melanophores of toads after the re-

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[5] The chromatosome-dispersing hormone can cause dispersion of the pigment-granules in the melanophores of certain reptiles such as lizards (e.g., *Anolis carolinensis* [Kleinholz, 1935]).

moval of all parts of the pituitary body is the result of the removal of the antagonistic influence of the pars tuberalis.[6]

According to Jores and Caesar (1935), pigment of the retina of the frog's eye assumes the dark position at a more rapid rate, if the eye be treated by a solution of the "melanophore hormone" in the dark. Similar treatment of the eye in the light only rarely is followed by an effect. Hypophysectomy, however, does not alter the movement of retinal pig-

TABLE 8

THE EFFECTS OF EXTIRPATION OF VARIOUS DIVISIONS OF THE PITUITARY
BODY ON THE CONDITION AND RESPONSE OF THE DERMAL MELANO-
PHORES IN *Xenopus laevis*[*]

CONDITION OF TOAD	MELANOPHORE-INDEX[†] ON		SENSITIVITY TOWARD MELANOSOME-DISPERSING HORMONE
	White Background	Black Background	
Normal.............................	1.4	4.5	++
After removal of the pars glandularis only.............................	1.4	4.5	....
After removal of the pars glandularis and the pars tuberalis..............	5.0	5.0	....
After removal of the pars intermedia and the pars neuralis..............	1.0	1.0	+
After removal of all parts of the pituitary body........................	1.8	1.8	+++

* From Hogben and Slome, Proc. Roy. Soc., London, B, **120**, 158–73 (1936).
† The higher the melanophore-index, the greater the degree of dispersion of the melanosomes, i.e., the greater the "expansion" of melanophores.

ment in response to light or darkness in either frogs (Jores and Caesar, 1935; Matuo, 1935) or toads (Okamato, 1937). Dubois-Poulsen (1937) also agreed that chromatosome-dispersing hormone facilitates the wandering of retinal pigment into the position characteristic of darkness.[7] The author used frogs (*Rana temporaria*) and concluded that epinephrine less effectively produces a change in the opposite direction.

[6] The authors also investigated the manner in which optic stimuli affect the background response. They concluded that the behavior of the melanophores of toads on white or black backgrounds depends upon retinal localization.

[7] See also Matuo (1935).

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New observations on the pharmacology of melanophores or of the melanosome-dispersing hormone.—Shen (1937) has studied the effects of a number of drugs on the behavior of the granules of pigment in the melanophores of the skin of frogs. Substances like F 933 and F 883[8] bring about marked dispersion of the melanosomes, provided that the pituitary is intact. After hypophysectomy, "expansion" of the melanophores does not appear. The conditions under which chloralosane, nicotine, or yohimbine cause melanosome dispersion are similar. Therefore, all these substances appear to act either by increasing the rate of secretion of the hormone or by markedly potentiating its peripheral effects or by both mechanisms. Shen found that melanosome concentration is reversed by F 933, if it is due to epinephrine but not if it follows stimulation of "pigmento-motor" nerves. Hence, in respect of a congregating effect on the melanosomes, he describes F 933 as a substance which is adrenolytic but not sympatholytic. The injection of either atropine sulphate or ergotamine tartrate into normal frogs adapted to a dark background is followed by paling;[9] in hypophysectomized frogs, however, either drug causes some melanosome dispersion. The author's experiments yield no specific information on the possible importance of effects on the secretion or peripheral action of a hormone of the pars tuberalis in relation to melanosome concentration. Hypophysectomy does not affect the dispersion of the melanosomes which is the result of the administration of amyl nitrite, chloroform, ether, or strychnine.

According to Jores (1935), the injection of extract containing melanophore hormone into rabbits by either an intraventricular or an intravenous route is followed by a fall in

[8] F 933: piperidino-methyl-3-benzodioxane; F 883: diethylamino-methyl-3-benzodioxane.

[9] The injection of ergometrine," Ephetonin" (synthetic ephedrine), or lobeline is followed by a similar effect.

body-temperature (0°.7–0°.8 C.) and a rise in the concentration of sugar in the blood. Atropinization or treatment by "Somnifen" lessened or abolished the apparent depressing effect on temperature. Both Jores (1936) and Parhon and Cahane (1936) reported that the repeated administration of epinephrine to rats is followed by an increase in the amount of melanosome-dispersing hormone in the pituitary body.[10] Jores attributed this change to a corresponding hypertrophy of the pars intermedia. In the mouse, on the other hand, a single large dose either of epinephrine or of "Cortidyn" (an extract of the adrenal cortex) caused an immediate reduction of the amount of melanosome-dispersing hormone in the pituitary. Jores also found that similar treatment of the rabbit or of man brought about an acute fall in the concentration of melanophore hormone in the blood. ("Cortidyn" alone or in combination with epinephrine had the same action in rats as epinephrine.)

Melanosome-dispersing hormone in relation to the metabolism of water.—The belief of some observers, such as Sulzberger, that the chromatosome-dispersing hormone (or some other new principle) of the pars intermedia is an agent capable of inhibiting diuresis cannot be accepted. Böttger (1936) even called this substance "adiuretin," but his evidence that it differed from the vasopressor principle of the pars neuralis consisted of comparisons of vasopressor and antidiuretic effects of extracts. Later (1937), he agreed that chromatosome-dispersing hormone is diuresis-inhibiting in proportion to its contamination by the vasopressor principle. Dischreit (1935) was unable to produce diuresis inhibition by "Intermedin" free from vasopressor hormone, although he used much larger doses, in terms of melanosome-dispersing hormone, than did Sulzberger. Fraser (1937) also was convinced that

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[10] Parhon and Cahane believed that testicular or corpus luteum hormone potentiates the action of melanosome-dispersing hormone, whereas thyroid hormone or oestrin is without such action.

the vasopressor principle is responsible for any antidiuretic effects of chromatosome-dispersing hormone.[11]

The metabolism of chromatosome-dispersing hormone.— Chromatosome-dispersing hormone can be detected in the urine of normal men and women. It appears with increased frequency in the urine of pregnant women; this fact, however, does not make tests for its presence of much value in diagnosing pregnancy (see p. 127, n. 5).

Lewis, Lee, and Astwood (1937) have extended the observations of others on the distribution of chromatosome-dispersing hormone in the pituitary body and adjacent structures of cattle. The unit used by them was the minimum amount of material causing an erythrosome dispersion in all fish (*Phoxinus laevis*) receiving that dose.[12] The error of assay apparently was high. Their estimate of the concentration of the hormone in various parts of the gland was as follows (all figures refer to units per gram fresh tissue): pus-like material in cleft consisting chiefly of desquamated cells of the pars intermedia, 270,000; pars intermedia, 255,000; colloid in cleft, 123,000; pars neuralis, 33,000; pars glandularis, 20,000–31,000; inferior part of stalk, 3,500; superior part of stalk, 300; tuber cinereum, 30; region about third ventricle, 12; cerebrospinal fluid, 0. The authors concluded that typical basophils could not be responsible for the secretion of the hormone by the pars intermedia, inasmuch as these were absent from that division of the gland. Their results are in agreement with the best data which had been gathered previously: in the pituitary of the ox, the chromatosome-dispersing hormone is secreted by the pars intermedia. Posterior-lobe extract contains the hormone because

[11] Jones and Steggerda (1935) could detect no change in the rate of loss of weight of frogs in water in relation to color adaptation to light, dark, or neutral backgrounds. In fact, hypophysectomized frogs lost weight at a similar rate.

[12] Böttger (1937) assayed chromatosome-dispersing hormone by using the isolated fin of male specimens of *Phoxinus laevis*. He observed microscopically the number of erythrophores affected as well as the degree of dispersion of the erythrosomes. Maximum effects occurred in 30–45 minutes. The error of determination was believed to be ±20 per cent.

it is commonly made from tissue containing the pars inter-
media and because the hormone readily diffuses into it and
into other parts of the pituitary body. It is interesting that
Lewis and his colleagues could furnish no support for the
view, which has been popular with some European authors,
that chromatosome-dispersing hormone may be secreted by
way of the stalk into the cerebrospinal fluid.

The chromatosome-dispersing hormone is secreted by cells
of the pars buccalis. In animals in which the pars intermedia
can be identified morphologically there can be little doubt
that that division of the pars buccalis secretes the hormone.
In animals like the whale in which no pars intermedia can
be found, the hormone can be extracted from the pars glandu-
laris (Geiling, 1935). Fisher (1937) reported that in the pos-
terior lobe of the pituitary of cats in which marked atrophy
of the pars neuralis had been produced experimentally, there
appeared to be no reduction in the amount of chromatosome-
dispersing hormone as determined by the response of the
melanophores of frogs or the erythrophores of the red-bellied
dace (*Chrosomus erythrogaster*).[13] The atrophied pars neuralis
contained no oxytocic or vasopressor (and diuresis-inhibiting)
hormone. The results of Geiling and Lewis (1935) also in-
dicated that the pars intermedia is the site of formation of
the chromatosome-dispersing hormone. The authors under-
took to make tissue cultures of the pars glandularis, the pars
intermedia, or the pars neuralis of the mouse and rat. The
pituitary of the mouse was preferred as a source of the tissues
because the various divisions could be separated more com-
pletely. After culture for 50 days, the pars intermedia con-
tained chromatosome-dispersing hormone but no vasopressor
hormone, indicating that the latter is not secreted by the
pars intermedia. Both hormones could be detected in cul-
tures of the pars neuralis not entirely free from pars inter-

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[13] Fisher was not satisfied that accurate results could be obtained by the use of
this fish.

media. Cultures of the pars glandularis contained neither chromatosome-dispersing hormone nor vasopressor hormone.

Jores (1935) was convinced that melanophore hormone accumulates in the pituitary of mice kept in darkness (1.45 units), whereas the amount falls rapidly when animals are exposed to light (0.27 unit). Responsibility for this change appeared to rest chiefly with light of shorter wave-lengths (blue), although exposure of mice to yellow and red light was followed by a slower and less pronounced reduction.

According to Rodewald (1935), if frogs are kept in darkness, their blood contains a substance "binding" chromatosome-dispersing hormone. The author believed that this substance is closely associated with the erythrocytes. It was not found in the blood of light or dark frogs exposed to light. Rodewald believed that two mechanisms operate to prevent any action of chromatosome-dispersing hormone in frogs kept in darkness: (1) no hormone is formed by the pituitary body,[14] and (2) a substance inactivating the hormone is liberated into the blood. Jores and Hoeltje (1936) believed that they confirmed the observation of Rodewald. Their results varied greatly and the differences found appear to be small. However, the authors reported that the blood of mammals (the rabbit and man) kept in darkness does not contain the inactivating substance but, on the other hand, seems to contain a higher concentration of the hormone itself. Later, Rodewald (1936) reported that the serum of patients with cancer contains a substance binding (or inactivating) melanophore hormone. Such a result was obtained by the use of the serum of 105 of 109 patients investigated (96 per cent). The reaction of the serum was positive in 2 of 50 pregnant women (4 per cent) but was negative in patients with carcinoma of the skin.

New observations on the chemistry of the chromatosome-dispersing hormone.—Among principles which can be extracted from

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[14] A change in the opposite direction was recorded by Jores, who used mice.

the pituitary body, none withstands chemical manipulation better than the chromatosome-dispersing hormone. The hormone is soluble in dilute aqueous solutions of acid or alkali and in certain organic solvents such as methanol and ethanol. Like the hormones of the pars neuralis, it is not destroyed by boiling in acidified water. However, it is remarkable that the hormone not only survives treatment by, or boiling in, fairly strong alkaline solutions, e.g., $N/10$, but also that its effects appear to be much more pronounced after this treatment, as was first shown by Hogben and Gordon. Böttger (1937) believed that after alkali has acted upon the hormone, the latter is metabolized more slowly, as shown by changes in the intensity and duration of its effects. According to Stehle (1936), the hormone is altered qualitatively, i.e., the initial effect is less intense but the duration of action is much longer. The degree of potentiation of the action of the hormone as a result of treatment by alkali has not been exactly defined. Stehle is of the opinion that it is much greater than Jores' estimate of 200–300 per cent. According to Abramovitz (1937), the chromatosome-dispersing effect of the pituitary of *Fundulus* is increased about twenty-five fold by boiling in $N/10$ NaOH.

It is probable that the same hormone causes dispersion of both melanosomes and erythrosomes. This view has recently been supported by Böttger (1937). New methods of purifying chromatosome-dispersing hormone have been described by Stehle (1936) and Böttger (1937). Stehle's product was about twenty-five times as active as International Standard Powder (posterior-lobe).

SUMMARY

The pituitary body or homologues of its divisions may be of great importance in the regulation of the distribution of pigment-granules in chromatophores of cold-blooded animals. Almost all the detailed studies are concerned with melanophores (fishes, amphibia, reptiles) and erythrophores (fishes).

Chromatosome dispersion is caused by a secretion of the pars intermedia or of the pars glandularis in animals otherwise lacking the anatomical equivalent of the pars intermedia.[15] The experiments of Hogben and Slome suggest that a secretion of the pars tuberalis causes the opposite effect— a concentration of the chromatosomes.

The significance of the chromatosome-dispersing hormone in vertebrates with functional chromatophores varies greatly. In some fishes, e.g., dogfishes, the hormone may be the principal means of chromatosome dispersion and, hence, of adaptation to dark backgrounds. In others, such as the catfish, nerves also play a part in melanosome dispersion. Finally, in a teleost fish like *Fundulus*, the hormone is present in the fish's pituitary but plays a negligible part in the regulation of chromatosome distribution, which is largely under the control of nerves. In the fish *Phoxinus laevis* the erythrophores and xanthophores are more specifically affected by the chromatosome-dispersing hormone than the melanophores. In amphibia like the frog the hormone appears to be the principal means of effecting dispersion of melanosomes. The action of the hormone in some reptiles—e.g., the lizard, *Anolis carolinensis*—may be similar, but its importance in normal animals has not been precisely investigated. Dispersion of either melanosomes or erythrosomes appears to be due to the same hormone.

The chromatosome-dispersing hormone can be extracted from the mammalian pars intermedia or pars glandularis. A substance with similar properties has been recovered from the blood and urine of mammals. If the substance has a function of importance to mammals, this has not been convincingly demonstrated. There probably is no foundation for the belief that melanosome-dispersing hormone can inhibit diuresis.

[15] The eye-stalks of crustacea appear to be homologous with the pars intermedia in this respect.

CHAPTER IX

NEW OBSERVATIONS ON THE CHEMISTRY AND PHARMACOLOGY OF EXTRACTS OF THE PARS NEURALIS

THE purpose of this chapter is to review recent investigations of the chemistry and pharmacology of extracts of the pars neuralis. There is no satisfactory additional evidence that more than two hormones—the oxytocic hormone and the vasopressor or diuresis-inhibiting hormone—are secreted by the pars neuralis. The advances which have been made in elucidating the cellular origin of the hormones are described in chapter i. The physiological importance of these hormones is discussed in chapter x.

The chemistry of the active principles.—The isolation of either the oxytocic or the vasopressor principle as a pure, crystalline substance is a goal yet to be attained. Stehle and Fraser (1935) have described new methods for separating and concentrating both hormones. However, these methods are too complicated for detailed review here. The authors found that, after the removal of most of the impurities, both of the hormones are soluble in 96 per cent methanol. Subsequent separation and concentration of the hormones was effected by the addition of ethyl acetate to solutions of both or one hormone in methanol (96 per cent) or ethanol (*ca.* 98 per cent). The pressor hormone was concentrated to about 100 times the value of International Standard Powder, the oxytocic hormone to about 125 times that value. Therefore, the potency of the preparations of Stehle and Fraser was about the same as that of the extracts of Kamm and his colleagues (1928). Tests for various amino-acids in the purified extracts were reported. The depressor substances in the posterior lobe were studied by Larson (1936), who attributed

most of the depressor action to histamine. This organic base, of course, was isolated from the posterior lobe years age.[1]

Gulland and others (1935) have particularly studied the oxytocic principle. They were unsuccessful in attempts to employ adsorbents to effect a high degree of purification. Electrodialysis also was found not to be of value. At pH 6.0–6.5 or less the hormone migrated toward the cathode; at a higher pH (8 or greater) the hormone remained in the central cell. No ultraviolet absorption spectrum characteristic of the hormone could be detected.

Gulland and Randall, Freudenberg, Weiss, and Biller, and Sealock and Du Vigneaud all published in the same year (1935) evidence that posterior-lobe hormone(s) contain an oxidation-reduction system probably dependent upon a disulphide linkage. According to Gulland and Randall, the E'_0 of the oxytocic principle is -0.025 volts at pH 6. They found the activity of the principle to be 100 per cent in the oxidized state and 50 per cent in the reduced state and offered an interpretation of this finding. Also, they suggested that there may be a second oxidation-reduction system in the molecule of the oxytocic hormone. Sealock and Du Vigneaud concluded that an -SH group, real or potential (-S-S-group), must be present in active extracts of either oxytocic or vasopressor hormone. Activity was preserved after reduction by cysteine or after reoxidation following such reduction but not after benzylation or methylation of the reduced compounds. The activity of the oxidized forms was not affected by treatment with methyl iodide or benzyl chloride. The activity of the oxytocic and vasopressor principles seems to be less dependent on the state of their oxidation-reduction systems than is the case with insulin.

The assay of the active principles of the pars neuralis.—In addition to the procedures reviewed previously, a few new methods have been employed for the assay of the hormones.

[1] It is not clear whether the chemical studies of Downes and Richards (1935) are of any significance.

Sealock and Du Vigneaud (1935) assayed the oxytocic principle by means of its depressor action on the blood pressure of fowls. As the authors point out, troublesome difficulties due to the action of foreign substances (such as those used for chemical manipulation of the hormone) may appear if the isolated guinea pig uterus be employed, whereas these substances may be without effect on the fowl's blood pressure. In addition, several authors have introduced refined methods of determining oxytocic effects both *in vitro* and *in vivo*.

For the assay of the vasopressor principle, Simon (1937) recommends that the effect on the blood pressure of the decapitated rat be determined. By this method as little as 0.0025–0.005 unit (0.00125–0.0025 mg. equivalent of International Standard Powder) can be detected. Small doses of histamine were found to be without action. The most sensitive test for vasopressor (diuresis-inhibiting) hormone is based upon the inhibition of water diuresis in the nonanesthetized dog. If the extract be given intravenously, as little as 0.0001–0.0003 unit may cause a recognizable effect.

The pharmacology of the oxytocic principle.[2]—Newton (1934, 1937) found that the cervix of the uterus of the pregnant goat or of the rat and guinea pig in pregnancy or in other stages of sexual activity is very insensitive toward the oxytocic principle in comparison with the uterine cornua. According to the findings of Li (1935), the isolated fallopian tube of the monkey is much more sensitive toward posterior-lobe extract during the secretory (corpus luteum) or menstrual phases of the uterus than during the proliferative (follicular) phase. Also, spontaneous activity of the fallopian tube tended to be lower during the growth of the ovarian follicle.

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[2] The intact, but not the isolated, uterus of the cat, dog, or rabbit relaxes and becomes quiescent in response to the administration of vasopressor hormone. This effect is most readily observed in animals which have received oestrogen previously and is said not to appear if the uterus is pregnant (cat and dog). Robson and Schild (1937) believed that the effect should not be attributed to the vascular action of the hormone (see also Azuma and Kumagai, 1935; Robson, 1936; and Morgan, 1937, as well as earlier reports previously reviewed.)

Nearly all the other observations on the pharmacology of the oxytocic principle were made to ascertain the uterine response after the secretion or injection of oestrogen or progesterone or both. For example, under the influence of oestrogen the uterus of some species of animals may exhibit a heightened sensitivity toward the oxytocic principle. Abortion, as shown by Parkes in the pregnant mouse, may occur after the administration of oestrogen followed by oxytocic principle, although either substance by itself does not interrupt pregnancy. To some authors (e.g., Druckrey and Bachmann, 1937) it has seemed that these and related observations satisfactorily explain the initiation of parturition and perhaps its continuation. However, the experimental basis for such a belief is far from satisfactory.[3] The later experiments of Marrian and Newton (1935) and of Robson (1935) in pregnant mice fully confirm Parkes's findings. The increased sensitivity to oxytocic principle after the administration of oestrogen can also be observed in the isolated uterus.[4] From experiments in other animals[5] such as the rabbit and man there is also evidence that both spontaneous activity of the uterus and its sensitivity toward the oxytocic principle are increased when follicular hormone (oestradiol) is predominantly affecting the uterus. The specificity of this increased sensitivity has not been proved. For example, ergotamine, like posterior-lobe extract, has been found to elicit uterine contraction more readily during ovarian follicular growth.

Undoubtedly, the uterus of the rabbit is less sensitive toward the oxytocic principle during pseudopregnancy or

[3] The reader is particularly referred to the articles of Marrian and Newton (1935), D'Amour and Dumont (1937), and Robson (1937).

[4] The isolated pregnant uterus of the mouse or rabbit is more sensitive toward the oxytocic principle after ovariectomy but not if the uterine contents also have been removed (Robson, 1936).

[5] Robson and Henderson (1936) reported that the oxytocin-sensitivity of the uterus of the hypophysectomized dog is, if anything, reduced after the administration of oestrin.

during much of pregnancy—an effect which is usually attributed to the internal secretion of the corpus luteum, progesterone. The effect can be produced in rabbits, spayed immediately after mating, by the injection of 4–5 mg. of natural or synthetic progesterone distributed over 5 days (Makepeace, Corner, and Allen, 1936). No corresponding decrease in the sensitivity of the urinary bladder or colon was observed by Podleschka and Dworzak (1936), who used posterior-lobe extract; their results, therefore, have no apparent significance. Robson (1935–36) found that it was difficult to demonstrate any change in the activity of oxytocic hormone on the uterus of pregnant or pseudopregnant rabbits as a result of the administration of oestrogen.

It is probable that the decreased oxytocin-sensitivity of the pregnant or pseudopregnant rabbit's uterus has no general significance. When the uterus of other animals is under the influence of the corpus luteum, there may be no evidence of diminished uterine sensitivity. This is true of the cat (van Dyke and Li, 1938), guinea pig (Bell and Robson, 1936), mouse and rat (Brooksby, 1937). From observations previously reviewed, as well as from new experiments, it may be concluded that the human uterus likewise is not less sensitive toward the oxytocic principle during the luteal phase of ovarian secretion. Although Kraul (1935) and Podleschka (1935) believed that the oxytocin-sensitivity of the uterus is reduced in the latter part of the menstrual cycle, their findings were not confirmed by the experiments of Kurzrok and others (1937), Miller, Cockrill, and Kurzrok (1937), and Robertson (1937).

Androsterone appears not to affect the sensitivity of the rabbit's uterus toward posterior-lobe extract (van Bokkum, 1936).

The pharmacology of the vasopressor hormone apart from its metabolic effects.—Following the intravenous injection of posterior-lobe extract or of an extract containing principally the vasopressor principle, a contraction of capillaries and arteri-

oles takes place as shown most simply by a rise in the blood pressure. The degree and the duration of the contraction depend to a considerable extent on the dose administered. Moreover, the vascular spasm produced may affect the coronary vessels, especially the left coronary artery,[6] so that tachycardia, disturbances of conduction, and cardiac dilatation appear. As a result, the blood pressure may fall initially but rises later as the coronary circulation is adequately reestablished and an increased or normal volume of blood is pumped against the increased peripheral resistance. This effect on the heart may or may not be observed, if small doses of vasopressor principle are used. If posterior-lobe extract is injected, it may be absent or less evident, perhaps because the oxytocic principle antagonizes the action of vasopressor principle on the coronary arteries.

According to Watrin and François (1937), repeated subcutaneous injections of posterior-lobe extract may be followed by cardiac hypertrophy in the guinea pig. The doses used (4–10 units on alternate days for 49–90 days) were large enough to cause convulsions occasionally. The maximum change observed was represented by a cardiac weight of 2.75 gm. (The weight of the heart of control animals was about 1.6 gm.) Enlargement of the heart was found to be due to hypertrophy, not hyperplasia, of the muscle fibers. The toxicity of vasopressor principle is known to be increased after the administration of thyroid extract, chiefly because of a change in cardiac response. Gruber, Moon, and Sufrin (1935) reinvestigated this problem by studying the electrocardiographic abnormalities in non-anesthetized rabbits. The histology of the hearts was also described.

Byrom (1937) injected enormous doses of vasopressor principle (5–40 units once or twice daily for 2 days or longer) subcutaneously into rats. Apparently marked arterial spasm locally gave rise to such pathological changes as infarction and necrosis in the kidneys, liver, etc. Like other authors,

[6] See the recent articles by Frommel and Zimmet (1937).

Byrom was impressed by the analogy between the effects of the vasopressor principle and the symptoms and pathology of eclampsia. Later (1938), he observed that the prior injection of oestrogen sensitized the rat toward the vasopressor principle, so far as the production of eclampsia-like changes in the kidneys are concerned. The author believed that this later finding strengthens the view that the vasopressor hormone is etiologically important in eclampsia.

Several authors have published new reports on the action of posterior-lobe extract or of purified vasopressor principle on the medulla[7]. If 5–10 units be injected intracisternally into the dog, a pressor effect immediately appears, probably because of stimulation of bulbar centers such as the vasomotor center. In comparison with intravenous injection, (1) the pressor effect is less pronounced but persists longer in terms of the rise in blood pressure and (2) a preliminary fall (coronary constriction) is not observed. It is probable that the effects cannot be attributed to the absorption of the hormone into the blood stream.

In the experiments of Daly, Mark, and Petrovskaia (1937) posterior pituitary extracts were added to the blood used to perfuse the lungs of dogs. A suitable period later it was found that there was a reversal of the usual action of epinephrine on the bronchi—i.e., broncho-constriction instead of broncho-dilatation was produced. This effect was prevented by ergotoxine. The extracts, of which "Pitocin" appeared the least active and "Pituitrin" the most active, also potentiated the action of epinephrine on the vascular system of the lungs.

Among new observations on the effects of posterior-lobe extracts on the eye are those of Holtz and Jancke (1936). Only the vasopressor principle was found to cause definite changes. For example, the instillation or subconjunctival injection of a large dose of the hormone (10 units) caused a

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[7] Van Bogaert, Sacchi (1935); Deleonardi, Seligsohn (1936).

fall in intraocular pressure and a miosis which was present after the administration of 2 drops of 1 per cent atropine sulphate. The fall in intraocular pressure apparently was due to vasoconstriction.

Reports on the action of posterior-lobe extract or of vasopressor principle on the movements of the gastrointestinal tract appear to require only brief mention.[8] Posterior-lobe vasopressor extract appears to be of considerable clinical value in stimulating peristalsis of the lower part of the small intestine and of the colon.

It seems unlikely that the enormous doses of vasopressor principle—e.g., 200 units subcutaneously in rabbits—used by Dodds and his colleagues to produce gastric lesions such as hemorrhage and ulceration are of any etiological significance in the formation of such lesions under other circumstances.[9] Large doses of posterior-lobe extract did not cause gastric lesions in the guinea pig (McFarlane and McPhail, 1937). Various studies of Dionessov (1936), Ejdinova (1936), Langeron, Paget, and Danès (1936), Merkulow (1936), and Cutting and others (1937) on the secretion of saliva, gastric juice, succus entericus, and pancreatic juice indicate that the effect of vasopressor principle is largely or entirely due to its vasoconstrictor action on the blood vessels supplying the glandular secreting cells.

The effects of posterior-lobe extracts on the metabolism of water and minerals.—The important changes in the metabolism of water and minerals following the injection of an extract of the posterior lobe are usually attributed to the vasopressor principle. In anesthetized or, under certain conditions, in non-anesthetized animals, the principal effect is an increased rate of urinary secretion which recently has been attributed to a change in the metabolism of salt, for which water is required for renal excretion. In non-anesthetized

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[8] De Biasio (1935), Guthrie and Bargen (1936), Melville, Necheles, and others (1936), and Frazier (1937). See also Schofield and Blount (1937).

[9] See also Laporta, Pepe, and Marinelli (1936).

mammals water diuresis is markedly and specifically inhibited by the vasopressor principle; simultaneously certain salts, particularly NaCl, are excreted at an increased rate. Diuresis inhibition usually is attributed to an increased reabsorption of water by the tubular epithelium of the kidneys (loop of Henle?). In addition, however, Fraser (1937) has found that the oxytocic principle appears to cause an increased secretion of urine in both "hydrated" and "nonhydrated" rats without clearly affecting the chloride in the urine. Fraser could not demonstrate any diuretic effect of oxytocic principle in the non-anesthetized dog with a fistula of the bladder. (Whether or not water was administered is not stated.)

The observations of Unna and Walterskirchen (1935–36) were made in non-anesthetized dogs with a permanent fistula of the bladder. Of particular interest is their report on *Leerdiurese*. The animals[10] were fasted 16–20 hours but were allowed water until 2 hours before the experiment. The injection of as little as 0.01 unit of posterior-lobe extract subcutaneously or 0.0001 unit intravenously could cause a definite increase in the excretion of Cl. If a diuresis appeared, it was thought to be caused by the Cl excreted. Both the Cl excretion and the diuresis were higher if the diet was high in Cl; likewise they were low in animals on a low Cl diet. Also Melville (1936) was of the opinion that a "salt-mobilizing" action is responsible for any diuretic action of vasopressor hormone. In anesthetized or non-anesthetized dogs, the diuretic effect of extract could be increased by the administration by mouth or by intravenous infusion under anesthesia of solutions of NaCl, KCl, or KNO_3 but not Na_2SO_4.[11]

Further investigations of the mechanism of the diuresis-

[10] Dogs weighing 6–12 kg.

[11] See also Frey (1937) for a discussion of factors influencing the diuretic action of posterior-lobe extract. Frey believed that increased glomerular filtration accounts for the change. It is not possible to state that this view is correct.

inhibiting effect of vasopressor principle (either as purified principle or as a simple extract of the pars neuralis) have been reported in the past few years by Samaan (1935), Handovsky and Samaan (1936), and Walker, Schmidt, Elsom, and Johnston (1937). Samaan confirmed previous observations on the lack of effect of renal denervation on diuresis inhibition due to the hormone. He found that posterior-lobe extract could cause very constant effects under standardized conditions. The extract caused no effect on the secretion of urine in dogs receiving repeated large doses of a solution of urea. The other authors reported on the behavior of the renal blood flow in non-anesthetized dogs and rabbits and in anesthetized dogs as revealed by the thermostromuhr. It appears that Handovksy and Samaan injected extract intravenously and found that the renal blood flow might or might not diminish during diuresis inhibition because of the extract. Walker and his colleagues used only non-anesthetized dogs and rabbits into which they injected extract subcutaneously. No change in renal blood flow occurred in association with the inhibition of diuresis.

If a large enough dose of vasopressor principle is injected subcutaneously into the non-anesthetized animal, hydremia is observed as in the experiments of Yanagi (1936). The author also found that the concentration of K in plasma is increased[12] and suggested that vasopressor extract brings about a transfer of water and K from the interior of cells to the extracellular fluid.[13] Anemia due to the injection of large doses of posterior-lobe extract was first reported by Dodds and his colleagues who used rabbits. It can also be produced in normal or hypophysectomized guinea pigs (Mc-

[12] According to Blazsó (1936), this change is observed in anesthetized animals, whereas the opposite change—i.e., decreased concentration of K in serum—takes place in the absence of anesthesia.

[13] The skin, which is important as a depot for chlorine, is believed by Toxopéus (1935) to deposit less of the element after the administration of NaCl if posterior-lobe extract also is injected. In addition, the author studied the chlorine of muscle without much success.

Farlane and McPhail, 1937). Gilman and Goodman (1935, 1937) attributed the effect to marked water retention, so that dilution of the blood renders the environment of the erythrocytes so unfavorable that a hemolytic anemia is produced. Using rats, Arnold and Marx (1937) observed hemoglobinuria which they also believed to be due to intravascular hemolysis. Arnold and Marx administered subcutaneously 15 units of posterior-lobe extract for each 100 gm. of bodyweight.

In patients with edema chiefly caused by renal disease considerable excess water can be removed during the diuresis which follows diuresis inhibition induced by vasopressor principle (McQuarrie, Thompson, and Ziegler, 1936). "Pitressin" was repeatedly injected, until the retention of water was represented by an increase of 3–4 per cent in weight. Administration of the hormone was then stopped abruptly. During the subsequent diuresis, edema fluid often was removed, especially if the diet was low in NaCl. The balance of NaCl was negative during both phases of renal secretion, whereas that of K, Ca, P, and N appeared not to be effected.[14]

It will be recalled that, if frogs are kept in water, the injection of posterior-lobe extract promotes the transfer of water through the skin (and perhaps its retention), so that the body-weight increases. In confirmation of earlier work, Oldham (1936) found that the oxytocic principle is 2.5–5.0 times as effective as the vasopressor hormone in causing this effect. The chromatosome-dispersing hormone probably is not a factor (Jones and Steggerda, 1935; Oldham, 1936). There is no agreement as to the action of posterior-lobe extract on the kidneys of the frog. Rey (1935) concluded that diuresis inhibition can be produced in either dry or wet frogs by a large dose of extract (about 1 unit injected into the

[14] See also the preliminary report of Smith and MacKay (1936), who studied the action of posterior-lobe extract on the intake and urinary excretion of NaCl in a normal man and in a patient with diabetes insipidus. Beltrametti (1935) believed that oestrogens or androgens favor the secretion of vasopressor hormone and thus are useful in the treatment of diabetes insipidus.

lymph sac). On the other hand, Granaat and Hillesum (1937) reported that doses of "Pitressin" which cause retention of water absorbed through the skin were without appreciable effect on the secretion of urine. If posterior-lobe extract produces anuria in frogs, it probably arrests the circulation of blood in the glomeruli (Adolph, 1936).

The effects of posterior-lobe extracts on the metabolism of carbohydrates.—It is not yet known to what substance the principal effects of posterior-lobe extract on carbohydrate metabolism should be attributed. In the rabbit, at least, extracts rich in the vasopressor principle usually appear to be the most powerful both in causing an elevation of the level of the blood sugar and in antagonizing the hypoglycemic action of insulin or the hyperglycemic action of epinephrine.[15] In this last case the vasopressor hormone perhaps facilitates liberation of insulin; however, there may be a simpler explanation such as an effect on the absorption of epinephrine. According to Ellsworth (1935–36), who confirmed the results of others in rabbits, it is the oxytocic fraction and not the vasopressor fraction which is responsible both for the production of hyperglycemia and for the antagonism of insulin in the dog. Moreover, Ellsworth found that the effect of the purified oxytocic extract in the dog was produced by much smaller doses (in terms of units) than are necessary to cause corresponding changes in the rabbit, which apparently is sensitive only to the vasopressor principle. Further studies are greatly needed to decide conclusively whether or not the action on carbohydrate metabolism is caused by some substance not identifiable otherwise.

Experimental work in animals indicates that hyperglycemia or insulin antagonism caused by posterior-lobe extract is the result of an action on the liver from which an increased quantity of glucose is liberated into the hepatic veins and thence into the general circulation because of glycogenolysis

[15] See the recent article of Gurd (1934).

(see reports such as those of Clark, 1928, and of Högler and Zell, 1935). However, it is the opinion of Cohen and Libman (1937), who performed their experiments in healthy men, that posterior-lobe extract lessens the utilization of glucose by the tissues and thus antagonizes the action of insulin. This belief arises from the following observations and reasoning: in comparison with the results of injecting only glucose, the injection of both glucose and posterior-lobe extract is followed by a longer and more pronounced rise in the level of the sugar of the blood; at the height of the effect the arteriovenous difference in the concentration of sugar in the blood is reduced; the arteriovenous difference in the level of the blood sugar is an index of the activity of insulin, which should be secreted at an increased rate in response to the hyperglycemia.

According to Ferrannini (1937), poisoning by phlorhizin in the rabbit affects only slightly the diuresis-inhibiting action of posterior-lobe extract. The latter in turn appears not to influence the glycosuria.[16]

Other effects of posterior-lobe extracts on metabolism.— Bühler (1935) reported that oxytocic extract can cause creatinuria in dogs or rabbits to disappear. In the toad, *Xenopus laevis*, neither the injection of posterior-lobe extract nor the removal of the pars neuralis seems to affect the creatine of muscle (Shapiro and Zwarenstein, 1937).

Blotner (1935) concluded that posterior-lobe extracts, after administration intranasally, prevent the rise—or even cause a fall—in the concentration of cholesterol in the plasma of patients with obesity or diabetes insipidus to whom 500 cc. of "20 per cent" cream had been given.

Some recent observations on the metabolism of the principles of the pars neuralis.—As is the case with anterior pituitary gonadotropic extracts, certain salts of metals delay absorption and thus prolong the action of the hormone(s). Dodds

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[16] The effect of posterior-lobe extract on the glucose, Cl, and protein of the blood of normal and diabetic persons was investigated by Dell'Acqua (1935).

and others (1937) demonstrated this phenomenon by observing the diuresis-inhibiting action of posterior-lobe extract with and without the addition of acetates of Zn, Ni, or Cd to the extract.

Jones and Schlapp (1936) found that both principles are metabolized alike after their intravenous injection in a large dose (about 20 units per kilogram body-weight) into decapitated cats. Within 20 minutes most of the hormones (85 per cent) had disappeared from the blood; there was none present after 2 hours. About 30 per cent of the extract in terms of vasopressor hormone could be recovered from the urine. The work of Heller (1937) indicated that, after the intravenous injection of posterior-lobe extract into the rabbit (and rat), the vasopressor hormone, measured by its diuresis-inhibiting effect, is excreted in the urine up to about 30 minutes after injection. Apparently, the amount excreted is not proportional to the dose but is limited because of unknown factors. Consequently, the higher the injected dose, the lower is the proportion of hormone recovered in the urine. Heller has found that blood adsorbs the hormone and has concluded that the kidney liberates the adsorbed hormone which is excreted at its point of action, the renal tubules.[17]

Certain tissues, especially the liver, can rapidly adsorb vasopressor hormone. According to Heller and Urban (1935), the adsorbing substance is heat labile and can be removed by animal charcoal. The hormone can be released from the adsorbent by boiling in saline solution. In addition, blood or liver contains an enzyme-like substance which destroys the hormone. Destruction by such a mechanism is rapidly accomplished by human blood, but not by cerebrospinal fluid. About 0.025–0.05 unit per cc. of blood is thus inactivated after 1.5–2 hours (see also Jones and Schlapp, 1936; and Heller, 1937).

[17] See also pp. 265–66, 278–79.

SUMMARY

Only two active principles have been identified as characteristic secretions of the pars neuralis: the oxytocic principle and the vasopressor or diuresis-inhibiting principle. It is not certain whether there is a third principle affecting carbohydrate metabolism. The oxytocic and vasopressor principles have been markedly concentrated and nearly completely separated from each other but are not yet available as pure substances. In both, an oxidation-reduction system dependent upon the disulphide linkage appears to be present; however, the state of this system seems to be much less important in determining activity than is true of insulin.

The physiological importance of these hormones is discussed in chapter x.

The oxytocic principle is usually more effective when the uterus is under the influence of oestrogen. In the rabbit the activity of the principle is markedly reduced if the condition of the uterus corresponds to that of pregnancy (except near term) and pseudopregnancy. However, this relationship is not found in other animals, including, probably, man. The important vascular effects of oxytocic principle appear to be (1) a depressor effect in birds and (2) possibly a relaxing effect on the coronary arteries. Recently it has been reported that the principle can promote diuresis in the rat.

The vasopressor principle is most important, not for its pressor action, but because it brings about water retention by facilitating the tubular reabsorption of water in the kidneys. It is difficult to describe the significance of its action on mineral metabolism. The hormone usually increases the rate of excretion of sodium chloride especially. Some evidence suggests that actions on tissues other than the kidneys are important; however, the findings so far are inconclusive. Larger doses of the vasopressor hormone are required to elicit a pressor effect, which initially may be masked by a fall in blood pressure caused by coronary constriction, which

in turn may markedly reduce the efficiency of the heart. Stimulation of peristaltic movements of the lower intestine and colon is produced by the vasopressor hormone. Also, the vasopressor hormone may cause an inhibition of movements and a relaxation of the uterus *in situ*. Very large doses of vasopressor hormone may cause anemia or lesions of the gastrointestinal tract. These effects probably are not of physiological interest. In the case of anemia, the change perhaps is due to facilitation of hemolysis by water retention. Lesions, especially of the stomach, probably are the result of a prolonged spasm of the organ's arterial supply.

Posterior-lobe extract may affect carbohydrate metabolism by (1) producing a moderate hyperglycemia, (2) antagonizing the hypoglycemic action of insulin, and (3) antagonizing the hyperglycemic action of epinephrine. The explanation of these phenomena cannot be satisfactorily given after a consideration of the data which have been published.

It is not yet possible to ascribe consistent effects on the metabolism of lipoids or proteins to extracts of the pars neuralis.

CHAPTER X

THE PARS NEURALIS AS A GLAND OF INTERNAL SECRETION

THE belief that the pars neuralis is an important gland of internal secretion has been greatly strengthened by recent experimental work on the physiological importance of the diuresis-inhibiting (or vasopressor) principle, confirming the earlier views of Starling and Verney, to mention only two of many investigators. Some of the reported experiments also indicate that secretion(s) of the pars glandularis is responsible or necessary for the marked polyuria and polydipsia accompanying the suppression of pars neuralis secretion. On the other hand, the importance of a secretion of the oxytocic principle has not yet been demonstrated and no data of great significance have been added to those previously reviewed. To a less extent this is also true of the possibly important vascular effects of the vasopressor principle.

Recent attempts to detect the active principles of the pars neuralis in cerebrospinal fluid or blood. New studies of the principles in the pituitary body.—Attempts to detect the active principles of the pars neuralis in cerebrospinal fluid have not met with convincing success. In a recent report Deleonardi (1936) concluded that oxytocic, pressor, and diuresis-inhibiting effects can be produced both by the cisternal fluid of the dog and rabbit and by the ventricular fluid (second and third ventricles) of the human cadaver but only exceptionally by human lumbar fluid. His observations on the oxytocic and pressor effects were not adequately controlled, because he failed to take into account the oxytocic effect of calcium ions in cerebrospinal fluid (he mentions that he employed a Tyrode's solution low in calcium for the uterine bath) and

because he did not recognize the possibility that cerebrospinal fluid may contain a pressor substance which is not identical with that of the pars neuralis (Page, 1935 and later). (The pressor substance described by Page is without effect after the complete destruction of the central nervous system.) Therefore, there remains from Deleonardi's observations the suggestion that cerebrospinal fluid may produce in rats, in a dose of 1 cc. per hundred gm., a slight diuresis-inhibiting effect similar to that following minute doses of pars neuralis extract. Levitt's observations (1936) must be added to those of others who, contrary to Anselmino and Hoffmann, have been unable to detect the diuresis-inhibiting (vasopressor) hormone in the blood of patients with hypertension or eclampsia. Simon (1937), using Marx's method, was unable to extract detectable quantities of vasopressor hormone from 100–200 cc. of human or canine blood (see also Neubach, 1937). The oxytocic effects of blood-extracts (women in second stage of labor, the pregnant cow, the rabbit before and after injection of pars neuralis extract) have been further investigated by Bell and Robson (1935). They concluded that the oxytocic effects of such extracts, if present, probably were neither caused by the oxytocic principle of the pars neuralis nor related to parturition.

Fisher and Ingram (1936) have shown that the atrophic pars neuralis of cats with diabetes insipidus due to a sufficiently extensive lesion of the supraoptico-hypophysial system contains only one-tenth or less of the normal total amount of the principal hormones of the pars neuralis. The concentration of active principles in the pars neuralis cannot be calculated from their data. The results of Fisher and Ingram are given in Table 9.

Jores (1935) reported that, if guinea pigs are kept in darkness for about 6 hours, the concentration of oxytocic and vasopressor principles in their pituitary bodies increases markedly. This observation was not confirmed by Simon (1936), who used guinea pigs, rabbits, and rats for his ex-

periments. Simon also found that the amount of hormones in the gland is not disturbed by the injection of posterior-lobe extract, thyroid extract, thyrotropic hormone extract, or insulin. Likewise, the amount of the vasopressor principle in the male guinea pig's pituitary is not altered following the injection of large doses of oestradiol benzoate or thyroxine (Schockaert and Lejeune, 1935). Determinations of the amount of oxytocic principle in the pituitary of adult and fetal sheep and pigs were made by Bell and Robson (1937). In terms of international units the pituitary of the adult sow contained 2–4.5 times as much oxytocic principle as that of

TABLE 9

	Total Units in Pituitary of		
	Pressor Activity	Diuresis-inhibiting Activity	Oxytocic Activity
Normal cats............	5.4 –7.5 (3)*	4.0 (1)	2.2 –3.5 (3)
Cats with diabetes in-sipidus..............	0.25–0.39 (4)	0.23–0.29 (2)	0.18–0.25 (4)

* The number of cats is indicated by the numerals in parentheses.

the adult ewe (14–32 international units compared with 7). The maximum amount of the principle in the gland of new-born animals ranged from 3–7 per cent of the figure for adults. The pituitary of young fetuses often contained much less.

Bickenbach (1936) could find no difference in the diuresis-inhibiting (and chloride-secreting) effects of the pituitaries of 2 patients with eclampsia compared with the effects of 2 normal human pituitaries.

The vasopressor principle.[1] *A. As a regulator of water metabolism in the body.*—Ranson and his co-workers have called attention to the work of von Hann (1918) who investigated the pathology of diabetes insipidus in several human cases

[1] Nearly all the evidence indicates that the diuresis inhibiting effects of pars neuralis extracts are due to the vasopressor principle.

and compared his results with the findings of others. Von Hann concluded that diabetes insipidus in man can occur only if (1) the pars neuralis is destroyed or severely damaged, (2) the pars glandularis is functionally active, and (3) there is no serious disorder of the heart and kidneys. Richter (1934) also maintained that diabetes insipidus in rats is readily produced, if all the posterior lobe but only part of the anterior lobe is removed. The majority of the recent reports support the von Hann–Richter hypothesis that typical diabetes insipidus requires the abolition of pars neuralis secretion but the persistence of pars glandularis secretion.

According to this hypothesis the development of diabetes insipidus may proceed in the following way. Either by disease or by experiment the internal secretion(s) of the pars neuralis no longer escapes into the blood or body-fluids. This may be accomplished by interruption of the secretory fibers from hypothalamic nuclei to the pars neuralis as by injury to the nuclei or to the supraoptico-hypophysial tract in the tuber cinereum or stalk, or by removal or destruction of the pars neuralis itself. Abnormal depletion (polyuria) of the body water then occurs, because the vasopressor hormone, which by its effect on the loop of Henle normally insures an adequate reabsorption of water during the secretion of urine, no longer finds its way into the blood. Compensation is then effected by the drinking of large amounts of water (polydipsia). Why, then, is a normally secreting pars glandularis also necessary for the maintenance of diabetes insipidus? Presumably a normal rate of formation of glomerular filtrate in the kidneys depends upon normal metabolic activity, which in turn depends to an important extent on the glands of internal secretion, particularly the thyroid. If the anterior pituitary, without whose secretion the principal other endocrine glands become inactive, is also removed, metabolic activity is reduced and probably abnormal. Consequently, a marked reduction in the volume and rate of formation of glomerular filtrate takes place, so that the lack of an adequate

reabsorption of water is masked and no clear-cut polyuria and polydipsia occur. A view favored by many is that the thyrotropic hormone, by its indirect effect on the thyroid, is chiefly responsible for the maintenance of a normal rate of glomerular filtration.[2] In the pages which follow the evidence in favor of the hypothesis just outlined as well as some observations to the contrary will be reviewed. Some of the best observations have been reported only recently and are impressive because of the care with which they have usually been made.

1. *The secretion of the vasopressor principle as a means of preventing dangerous loss of body water.*—Gilman and Goodman (1936–37) performed a series of interesting experiments in rats. They found that, if water and food were withdrawn from normal rats, the rate of secretion of the urine, of course, fell, depending upon the period of thirst. At the same time diuresis-inhibiting effects, analogous to those produced by pars neuralis extracts, could be secured by injecting suitably prepared urine. The amount of diuresis-inhibiting principle present increased as the period of water withdrawal was prolonged, so that the equivalent of as much as 5 units of hormone was excreted by 20 rats during a period of 72 hours without water.[3] No detectable amounts of the principle could be discovered in the urine of rats drinking water *ad libitum*. If rats were hypophysectomized and then subjected to water-withdrawal, they secreted three times as much urine as normal rats treated similarly; no diuresis-inhibiting hormone could be found in their urine. Control experiments indicated that the procedure used was suitable for identifying diuresis-inhibiting (vasopressor) hormone. Moreover, the diuresis-inhibiting substance in the urine of rats receiving

[2] Another possibility, in favor of which there is little evidence, is that a secretion of the pars glandularis has diuretic effects not mediated through another gland of internal secretion. White and Heinbecker suggested that a secretion of the thyroid sensitizes the animal toward an anterior pituitary diuretic factor.

[3] Diuresis caused by the administration of a solution of NaCl to rats from which water was withheld likewise was characterized by the rapid appearance of diuresis-inhibiting principle in the urine.

no water was destroyed in strong solutions of acid or alkali, as is that in an extract of the pars neuralis. The conclusions of Gilman and Goodman from these experiments seem logical. The amount of vasopressor or diuresis-inhibiting principle secreted by the pars neuralis fluctuates with the body's need for water conservation. Normally, the amount secreted is so small that none can be detected in the glomerular filtrate. If there is a shortage of water, its retention in the body is largely due to a reduction in the volume of urine secreted. And the emergency secretion of an increased amount of diuresis-inhibiting hormone by the pars neuralis is perhaps the important means of accomplishing this by increasing the reabsorption of water in the renal tubules. The unusual amount of hormone secreted filters in part through the glomeruli and can then be detected in the urine.

2. *The importance of hypothalamic nuclei, especially the supraoptic nuclei, for maintaining the secretion of the vasopressor principle.*—In several recent reports of experiments in cats and monkeys, Fisher, Ingram, and Ranson[4] have shown that the supraoptic nuclei of the hypothalamus may be essential not only to liberate suitable amounts of vasopressor hormone —to prevent undue loss of water by way of the kidneys— but also to maintain the pars neuralis anatomically. Cats were used for most of their experiments. Employing the Horsely-Clarke stereotaxic instrument as a means of placing lesions in different parts of the hypothalamus, they produced a severe permanent diabetes insipidus in a number of cats.[5] Later, sometimes after months of severe diabetes insipidus, the animals were killed, and the hypothalamus and pituitary

[4] Fisher, Ingram, Hare, and Ranson (1935), Fisher, Ingram, and Ranson (1935), Fisher and Ingram (1936), Ingram and Fisher (1936), Ingram, Fisher, and Ranson (1936).

[5] The diabetes insipidus appeared about 8–12 days after a suitable lesion(s) had been made. Polyuria appeared to precede polydipsia (see also Fisher, Magoun, and Hetherington, 1938). In addition, a transient polydipsia and polyuria were commonly observed immediately after operation. These initial transient changes have been observed by a number of authors using different animals. Usually they are attributed to an effect on the nervous system alone.

body were carefully studied anatomically to determine how the lesions found could be correlated with animals' symptoms. As a result of this study, the authors have reached the following conclusions:[6] (1) diabetes insipidus is due to a deficiency of pars neuralis secretion, presumably the vasopressor principle; (2) the secretion of the pars neuralis is not formed and liberated unless at least one supraoptic nucleus is functionally active and connected with the pars neuralis. The fibers from the supraoptic nuclei to the pars neuralis appear to be efferent. If the tract(s) is interrupted, the nerve cells of the nuclei degenerate. The anatomical changes in the hypothalamic-hypophysial region accompanying diabetes insipidus may be due to (a) a lesion causing destruction of both supraoptic nuclei, (b) a lesion interrupting the tract fibers arising from both nuclei as in the tuber cinereum or the stalk, or (c) destruction or removal of the pars neuralis; lesions (a) or (b) are followed by atrophy of the pars neuralis. (3) The pars tuberalis and probably the pars intermedia are of no significance in the genesis and maintenance of diabetes insipidus; and, finally, (4) the pars glandularis probably is important or essential, if pronounced diabetes insipidus occurs.

The relationship of hypothalamic nuclei to the pituitary as well as the most convenient position in which suprapituitary lesions can be placed to produce diabetes insipidus are illustrated in Figures 27 (cat) and 4 (monkey). Destructive lesions of the mammillary bodies or of nuclei other than the supraoptic nuclei (such as the paraventricular nuclei, the ventrolateral hypothalamic nuclei, etc.) are not followed by diabetes insipidus.

Farr, Hare, and Phillips (1937), using cats, have confirmed the observations of Ranson and his colleagues. In reports of the anatomical changes in 4 human cases of diabetes in-

[6] The conclusions refer to the experiments of Fisher, Ingram, and Ranson. The authors do not hold that other mechanisms for producing diabetes insipidus—especially in other animals—do not exist.

sipidus, Biggart (1935–36) also observed changes in the su-
praoptic nuclei and stalk consistent with the views expressed
by Fisher, Ingram, and Ranson. There is little evidence to
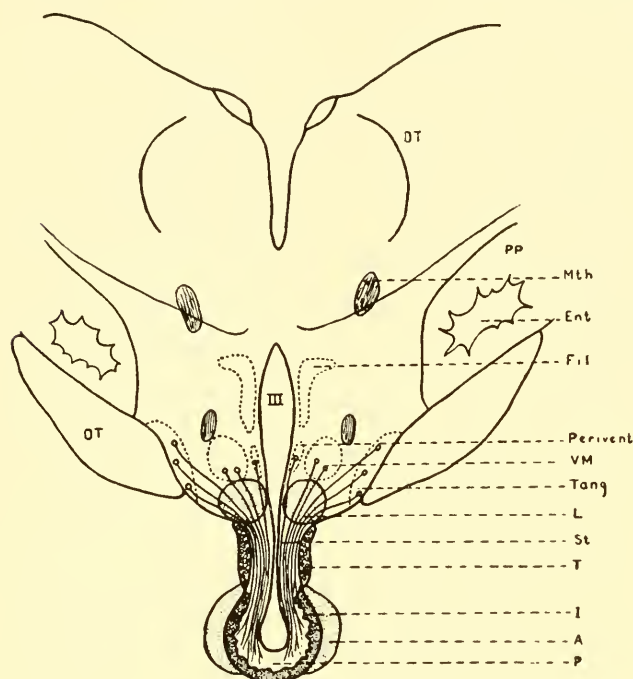
Fig. 27.—One position in which bilateral lesions of the hypothalamus can be
placed to produce diabetes insipidus in the cat by interrupting fibers of hypothala-
mic hypophysial tracts. (From Fisher, Ingram, and Ranson, Arch. Neurol. Psy-
chiat., **34,** 124–63 [1935].)

A: pars glandularis; *Ent:* entopeduncular nucleus; *Fil:* filiform (paraventricu-
lar) nucleus; *I:* pars intermedia; *L:* lesion as stippled area; *Mth:* mammillothalamic
tract; *OT:* optic tract; *P:* pars neuralis; *Perivent:* periventricular nucleus; *PP:*
pes pedunculi; *St:* stalk; *T:* pars tuberalis; *Tang:* caudal part of tangential (supra-
optic) nucleus; *VM:* ventromedial hypothalamic nucleus.

favor Biggart's opinion that the pars tuberalis is etiologically
important in diabetes insipidus. There is still less justifica-
tion for his belief that diuresis inhibition by the vasopressor
principle depends to an important extent on an action of the
hormone on tuberal nuclei (in Biggart's Case 5 the polyuria

"was not controlled by injections of pituitrin"). The report of Adlersberg and Friedmann (1935) deals with changes in the metabolism of water, under various conditions, in patients with lesions of the mesencephalon or diencephalon or both. In some instances the response to posterior-lobe extract was clearly diminished. Keller, Noble, and Hamilton (1936) stated that a "complete" separation of the pituitary from the hypothalamus (including "the greater portion of the infundibulum") in the dog is not followed by any increased water or food consumption by the animals. More recently, Keller and Hamilton (1937) observed complete degeneration of the nerve fibers in the pars neuralis as a result of lesions of the tuber cinereum in 7 cats. In 4 of the cats there was no diabetes insipidus; the authors concluded that degeneration of the nerves of the pars neuralis—contrary to the views of Ranson and his colleagues—is not necessarily accompanied or followed by diabetes insipidus. Other data of less recent origin, some of which also can be interpreted as opposing the beliefs of Fisher, Ingram, and Ranson, have been reviewed already (van Dyke, 1936).

3. *To what extent does diabetes insipidus depend upon a functioning pars glandularis?*—The hypothesis of von Hann, supported by the later experimental work of Richter, has already been discussed (pp. 276–77). It is proposed here to review briefly a number of recent communications bearing on this question.

In a few reports diabetes insipidus—or the secretion of an increased volume of urine—has been observed in completely hypophysectomized animals (toad: Pasqualini, 1935; rat:[7] Dodds, Noble, and Williams, 1937; dog: Page and Sweet, Reichert and Dandy, 1936). On the other hand, Buratschewski and Rappoport (1936) found that the metabolism of salt and water in the dog was not disturbed by either hypophysectomy or the removal of the pars neuralis. Such data contradict most of the recent findings of others.

[7] See also Sandberg, Perla, and Holly (1937).

The work of Pencharz, Hopper, and Rynearson (1936) in the rat as well as that of Keller, Noble, and Hamilton (1936) and of White and Heinbecker (1937) in the dog and that of Dodds and his colleagues in the cat (1937) indicate that diabetes insipidus follows the excision of the pars neuralis, but that it promptly ceases if the pars glandularis is later removed. Pencharz and others were unable to provoke polydipsia in completely hypophysectomized rats by repeatedly administering homo-implants (1–3 anterior lobes on alternate days for 3 weeks). However, Keller (1937) observed a dog whose diabetes insipidus disappeared as a result of complete hypophysectomy. Inasmuch as the diabetes insipidus reappeared following the administration of anterior-lobe extract or the feeding of thyroid extract, Keller concluded that the maintenance of polyuria in dogs with an intact anterior lobe is due to the thyrotropic hormone. White (1937), like Pencharz and his colleagues, was unable to cause, by the administration of anterior pituitary extract,[8] any convincing change in the amount of urine secreted by rats from which the pars neuralis or the whole pituitary had been removed a year previously . The administration of thyroid extract with or without the injection of anterior-lobe extract likewise was without significant effect.[9] Other experiments of White and Heinbecker (1937) in dogs led to the conclusion that the pars glandularis secretes a diuretic principle which is not thyrotopic hormone but, nevertheless, at first is ineffective in the absence of the thyroid. After the removal of the thyroid from the dog, the diuretic effect of anterior pituitary extract gradually reappeared, perhaps, as the authors suggest, owing to regeneration of thyroid tissue or to some unknown readjustment. Hypophysectomized or normal dogs were about equally sensitive toward the diuretic

[8] White injected an acid extract of beef anterior lobe.

[9] Farr, Hare, and Phillips (1937) stated that cats with diabetes insipidus caused by lesions of the supraoptico-hypophysial tract exhibited a pronounced increase in the polyuria, if a saline suspension of beef anterior lobe had been injected.
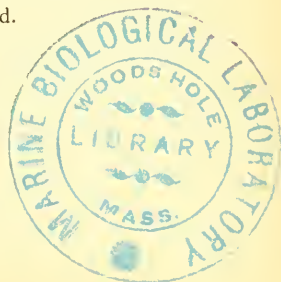
action of anterior pituitary extract.[10] Thyroid extract caused no change in the metabolism of water either in thyroidectomized or in hypophysectomized-thyroidectomized dogs. As a result of their experiments in cats and rats, Dodds, Noble, and Williams (1937) also suggested that the diuretic action of anterior pituitary secretion after the removal of the posterior lobe is not due to thyrotropic hormone.

Evidence from other types of experiments speaks more in favor of than against the belief that a secreting thyroid gland is responsible to an important extent for the polyuria of diabetes insipidus. It is necessary also to bear in mind that the importance of the thyroid gland may vary in different animals. Mahoney and Sheehan (1935) occluded the pituitary stalk in dogs by means of a silver clip. The subsequent severe polyuria and polydipsia could be abolished by thyroidectomy and later re-established by the feeding of thyroid extract. The removal of the thyroid in cats with diabetes insipidus caused by a lesion of the supraoptico-hypophysial system "may somewhat reduce but does not abolish the polyuria" (Fisher and Ingram, 1936; Ingram and Fisher, 1937). On the other hand, the feeding of thyroid to such cats causes a marked diuresis; after the withdrawal of thyroid-medication, the polyuria may be as great as before thyroidectomy. Findley and Heinbecker (1937) completely removed the thyroid from a man with syphilis of the central nervous system and with diabetes insipidus. The important changes observed subsequent to the operation were some reduction of the polyuria when the amount of salt in the diet was high or unrestricted and some increase in the diuresis-inhibiting effect of "Pitressin" (see also Findley, 1937).

4. *Miscellaneous observations.*—According to Pickford (1936) as well as others, the action of posterior-lobe extract after intravenous administration is, within certain limits, inversely proportional to the "water load" of the body. This

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[10] The extract sometimes caused an initial decrease in the rate of formation of urine. This always occurred in the monkey and might be the only change observed.

conclusion was based upon experiments in dogs with intact pituitaries. Presumably more vasopressor hormone was secreted as the water load diminished.

By means of acute experiments in rabbits which had received neither food nor water for 24–48 hours, Janssen (1935) found that afferent stimuli could cause an increased rate of secretion of urine in which the concentration of chloride rose. The fact that this effect occurred after renal denervation led to the conclusion that it was due to the reflex secretion of a hormone. Theobald and Verney (1935) measured the action of afferent stimuli[11] on the secretion of urine by the denervated kidney of the dog in which diuresis was provoked by water. Inhibition of diuresis was readily produced and sometimes persisted for 5–20 minutes after the removal of the stimulating agent. The authors concluded that the diuresis inhibition was not caused by epinephrine and suggested that the hormone responsible for the effect was secreted by the pars neuralis. This suggestion seems logical and is in agreement with both the earlier work of Verney and his colleagues and with nearly all recent observations.

Brull (1937) concluded that an unknown pituitary principle (not those recognized in the pars neuralis and neither gonadotropic nor thyrotropic hormone) can lower the threshold of renal excretion of inorganic phosphate, provided that the parathyroid hormone is also present.

The vasopressor principle. B. As a regulator of the cardiovascular system.—Blount (1935) transplanted two pituitary anlagen (including the future pars neuralis) into individual urodele larvae, *Amblystoma punctatum*, and concluded that the symptoms appearing later were analogous to hypertension in man. He based this conclusion particularly on the reduction in the size and number of the peripheral capillaries associated with "labored attempt(s) at propulsion of corpuscles" and an "increased back-flux of diastole." The heart

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[11] E.g., by the insertion of a hypodermic needle in the region of the fourth lumbar interspace.

rate was found to be reduced; also, there were enlargement of the heart and hypertrophy of the ventricular wall. Because of contraction of the vessels, the spleen was less than half the normal size. The glomeruli of the kidneys resembled those of hypertension in man. The profound peripheral vascular disturbance apparently interfered with the growth of some of the peripheral structures. Blount also had the impression that the vascularity of the structures studied was increased after hypophysectomy.

All the other observations indicating that the cardiovascular effects of pars neuralis secretion may be physiologically important have been made in mammals. Chang and his colleagues (1937) discovered that stimulation of the central end of the vagus in the dog whose head is connected with the body only by blood vessels, causes a rise in blood pressure resembling that following the injection of vasopressor principle. The effect could be abolished either by hypophysectomy or by cutting the pituitary stalk. Thus it appears that a reflex secretion of vasopressor principle can be demonstrated in the dog. The vagus nerve is the only part of the afferent arc known at present; probably the terminal efferent arc is the supraoptico-hypophysial tract. The experiments of Schockaert and Lambillon (1935–36), although of more deductive significance, are also of considerable interest. They showed that the serum of pregnant women seemed to bind or inactivate, i.e., prevent, the vasopressor effect of a pars neuralis extract in the decapitated cat. Later they demonstrated that the intravenous injection of 5 units of a purified solution of the vasopressor principle ("Tonephin") caused much more severe symptoms such as precordial and abdominal pain, vomiting, and involuntary defecation in normal women than in women in the last third of pregnancy. The average elevation of the systolic blood pressure in non-pregnant women was 43 mm. Hg.[12] In the pregnant women, the

[12] In spite of the recent statement of Gilman and Goodman (1937) that ". . . . in unanesthetized dogs and humans, pituitary extract is not pressor," this observation

injection caused an average elevation of 15 mm. Hg in the systolic blood pressure; only rarely were symptoms other than paleness of the face and cyanosis of the lips present. These observations suggest that the diminished response of pregnant women to the vasopressor principle is due to a substance liberated into the blood. Whether or not a disturbance in its formation may be etiologically important in eclampsia, as Schockaert and Lambillon suggest, is unknown.

The experiments of Anselmino and Hoffman were the basis for the attractive hypothesis that the reduced urinary secretion and the hypertensive symptoms of certain diseases such as eclampsia and essential hypertension are due to a "hypervasopressinemia." However, satisfactory confirmatory data are almost entirely lacking. Dieckmann and Michel (1937) as well as others have pointed out that the pregnant woman in the pre-eclamptic condition is markedly hypersensitive to the pressor effect of pars neuralis extract; moreover, they concluded that this abnormal response constitutes a useful diagnostic test for pre-eclampsia, but that it is not free from danger. Byrom (1938) has suggested that abnormally large amounts of free oestrin may circulate in the blood of patients with eclampsia and that this oestrin synergizes with vasopressor hormone in causing the important pathological changes (see pp. 263–64). According to Coester (1935), purified extracts of urine from normal individuals or from patients with two varieties of hypertension produced about the same diuresis-inhibiting and pressor effects. Still other observations have been made by Jores (1936), who concluded that abnormal amounts of anterior pituitary hormones stimulating the adrenals (cortex and medulla) circulate in the blood in certain hypertensive disorders, such as essential hypertension and pituitary basophilism (Cushing), and that these

and others which have been made before indicate that man, like other animals, exhibits a clear-cut pressor response to intravenous injections of pars neuralis extracts.

hormones are causally related to the symptoms.[13] Van Bogaert (1936) was convinced that neither the pituitary nor the adrenals is etiologically important in hypertension but that the pituitary may be important in maintaining the symptoms.

The relationship between the pituitary and the experimental hypertension due to renal ischemia produced by the clamp of Goldblatt and others has been investigated in the dog by Page and Sweet (1936–37). In normal animals hypophysectomy caused some reduction of the arterial blood pressure. In dogs in which hypertension (240/160 mm. Hg) had been produced by means of Goldblatt's clamp, the high level of arterial pressure was maintained for several months unless hypophysectomy was performed. Some weeks after hypophysectomy, the blood pressure fell, sometimes nearly to normal (150/100 mm. Hg), sometimes below normal (90/40 mm. Hg). Subsequent further constriction of the renal arteries again produced a rise in blood pressure which tended to be transient. The administration of thyroid extract also might be followed by a moderate increase in arterial pressure (see Fig. 28). The authors concluded that the effects of hypophysectomy were indirect and depended probably upon the removal of the pars glandularis without which the thyroid and adrenal glands performed their functions imperfectly. It is regrettable that this interpretation was not strengthened by observing the effects of extirpation of either the pars glandularis or the pars neuralis alone, because their observations do not satisfactorily exclude the possibility that the pars neuralis plays some part in maintaining the hypertension. Page (1936) was not able to detect any increased amount of hypertensive principle in the blood of dogs with the hypertension of renal ischemia; however, his method of

[13] Positive results were obtained in 20 of 28 patients with essential hypertension and in 6 with Cushing's syndrome. The findings were negative in 8 patients with eclampsia or renal disease of pregnancy.
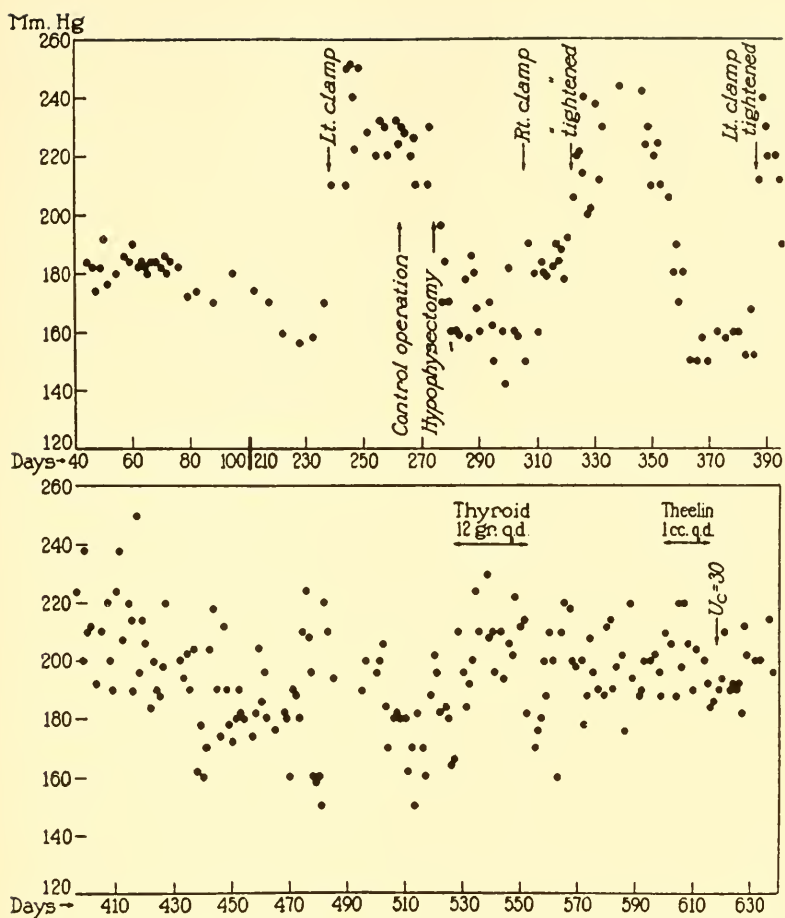
Fig. 28.—The relation of the pituitary body to hypertension caused by renal ischemia following the application of Goldblatt's clamp to the renal arteries. (From Page and Sweet, Amer. J. Physiol., **120,** 238–45 [1937].)

Ordinate: arterial blood pressure; abscissa: time in days. Without hypophysectomy, the hypertension following the application of the first clamp probably would have persisted some months. Hypertension subsequently produced by tightening the right and left clamps was transient. The administration of thyroid gland in other experiments caused a recurrence of the hypertension.

making extracts (alcoholic extracts of plasma) may not have been suitable for the pituitary vasopressor principle.

The oxytocic principle.—The additions to our knowledge of the possible physiological importance of the oxytocic principle in parturition are, for the most part, only of inferential value. Newton (1937) found that the isolated cervix uteri of the rat and guinea pig, in any stage of sexual activity including pregnancy, is very insensitive toward the oxytocic principle (concentration of 40 units per liter of bath-fluid). Newton considers that this fact strengthens the evidence favoring the importance of oxytocic-principle secretion in normal parturition. Possibly important interrelationships between the secretion of oestrogens or progesterone and the action of the oxytocic principle are discussed on pages 261–62. According to Ingram and Fisher (1937), if diabetes insipidus is produced in pregnant cats by a lesion of the supraoptico-hypophysial system, the subsequent parturition is incomplete and terminates in death. However, others (including Houssay, 1935, and Robson, 1936–37) have demonstrated that normal parturition can take place in the cat, dog, mouse, rabbit, and rat after the removal of the posterior lobe or after hypophysectomy. This fact must be taken into account if the initiation or continuation of labor is to be explained as the result of oestrogen-sensitization of the uterus toward the oxytocic principle or if the interference with parturition observed by Ingram and Fisher is to be ascribed to a deficiency in the secretion of the oxytocic principle.

The pars neuralis and menstruation.—Hartman and Firor (1935) have again suggested that menstruation possibly requires a functioning pars neuralis. However, the evidence offered does little to commend this hypothesis: of four immature monkeys in which complete hypophysectomy was attempted, the operation was successful in only one; "oestrin-deprivation" bleeding after 640 rat-units of oestrin was observed in all the animals except the one completely hypophysectomized. In the experiments of Smith, Tyndale, and

Engle (1936), 400–500 rat-units of oestrin were injected daily for 10 days into young or adult hypophysectomized monkeys. After injections were stopped, delayed bleeding was observed in 8 instances. In 2 instances bleeding did not occur. The authors were loath to attribute the delay in or absence of bleeding to a specific factor.

SUMMARY

Contrary to the view previously expressed (van Dyke, 1936), there is now good evidence that the pars neuralis is an important gland of internal secretion. The best data have been gathered in studies of the metabolism of water. In the normal mammal, it seems probable that the reclamation of water filtered through the glomeruli of the kidney when urine is secreted depends upon the diuresis-inhibiting (vasopressor) hormone of the pars neuralis. If a dangerous loss of water from the body is threatened, diuresis-inhibiting hormone is secreted at an increased rate and by its local action on the tubular epithelium of the kidneys increases the rate of re-absorption, and hence the conservation, of water. The nervous control of the secretion of diuresis-inhibiting hormone appears to be of the greatest importance and explains how afferent stimuli can affect (inhibit) the secretion of urine after renal denervation. In an animal like the cat the paired supraoptic nuclei of the hypothalamus apparently supply most of the secretory fibers of the pars neuralis which undergoes atrophy and secretes little or no hormone if the nuclei have been destroyed or the fibers have been cut, as after section of the stalk. Under such circumstances, the kidneys lose their ability to concentrate urine, so that water loss, polyuria, is abnormally rapid. In compensation the animal drinks an increased volume of water (polydipsia). The changes, therefore, are analogous to diabetes insipidus in man.

Furthermore, it appears that the function of another part of the pituitary, the pars glandularis, is necessary for the

complete development of diabetes insipidus. Generally, it has been found extremely difficult to produce diabetes insipidus after complete hypophysectomy, whereas, if the pars glandularis is intact, the suppression of posterior-lobe secretion readily produces that condition.[14] (Also, if diabetes insipidus has been produced, it can be abolished by removal of the pars glandularis.) Most observations indicate that the thyroid gland also must be intact. However, it is not certain that the diuretic principle of the anterior pituitary is identical with thyrotropic hormone.

Diuresis-inhibiting hormone facilitates the excretion of certain cations and anions, especially Na and Cl. Future work will have to decide what is the best interpretation of this phenomenon in terms of the physiological importance of the hormone.

Whether or not the vasopressor hormone is physiologically important because of its cardiovascular effects is not known. Recently it has been shown that the hormone probably is liberated by stimulation of the central end of a vagus nerve. Its possible clinical significance in disorders like hypertension and, especially, eclampsia, however great it may be, has not been demonstrated.

In view of the highly specific action of the oxytocic principle on the uterus, it is to be expected that new observations on its importance in normal parturition will be gathered. At present it appears that the hormone, i.e., the pars neuralis, is not necessary for parturition. It is possible that parturition in normal animals may be greatly facilitated by its action, perhaps in synergism with oestrogen.

Although changes in the metabolism of carbohydrates can be produced by posterior-lobe extracts, it is not possible to state whether these effects are physiologically important.

[14] It is to be hoped that older observations indicating that diabetes insipidus can be produced by hypothalamic lesions after complete hypophysectomy will be either disproved or confirmed, so that they can be evaluated.

APPENDIX

THE STRUCTURAL FORMULAS AND PRINCIPAL ACTIONS OF HORMONES OF NATURAL ORIGIN

Notable advances have been made in isolating and determining the structure of hormones and of substances necessary for their synthesis or produced in their degradation. Moreover, a number of synthetic hormones has been made. The skill of chemists has been most fruitfully applied in studying substances with a nucleus derived from cyclopentenophenanthrene.

The table and formulas of the Appendix deal only with hormones or related substances of natural origin and of known structure. Although the list is believed to be complete at this time, it undoubtedly will be lengthened as a result of future research. The substances are listed alphabetically in the table which includes data believed to be of greatest interest to readers of this book. The formulas likewise are arranged alphabetically and follow the table.

TABLE 10

Hormones or Related Substances of Natural Origin

(In every instance the structural formula is known)

No.	Hormone or Related Substance	Principal Action	Source	Hormone-Relationship if Inactive	Unit (As Mg.)				
					Mouse	Rat	Rabbit	Capon	International
1	Allopregnanediol	Inactive	Urine of pregnant women	Corpus luteum hormone	......	......	......	......	......
2	Allopregnanolone	Inactive	Corpora lutea of sows	Corpus luteum hormone	......	......	......	......	......
3	Androsterone	Androgen	Urine of men	......		......	......	0.15–0.20	0.1
4	Corticosterone	Of adrenal cortical hormone	Adrenal gland		......	......	......	......	......
5	Dehydroisoandrosterone	Androgen	Urine of men		......	......	......	0.6	......
6	Dihydroequilenine	Oestrogen	Urine of pregnant mares	......	0.003	......	......	......	......
7	Epi-allopregnanol-3-one-20	Inactive	Urine of pregnant women	Corpus luteum hormone	......	......	......	......	......
8	Epinephrine	Hormone of adrenal medulla	Adrenal gland	......		......	......	......	......
9	Equilenine	Oestrogen	Urine of pregnant mares	......	0.0015	......	......	......	......

TABLE 10—*Continued*

No.	HORMONE OR RELATED SUBSTANCE	PRINCIPAL ACTION	SOURCE	HORMONE-RELATIONSHIP IF INACTIVE	UNIT (AS MG.)				
					Mouse	Rat	Rabbit	Capon	International
10	Equilin	Oestrogen	Urine of pregnant mares		0.0008				
10A	Hippuline*	Oestrogen	Urine of pregnant mares		0.0008				
11	α Oestradiol	Oestrogen	Urine of pregnant mares and liquor folliculi of sow ovaries			0.0001			
12	β Oestradiol	Oestrogen	Urine of pregnant mares			0.003			
13	Oestriol	Oestrogen	Urine of pregnant women		0.013				
14	Oestrone	Oestrogen	Urine of pregnant women and mares and of stallions			0.001			0.0001
15	Pregnanediol	Inactive	Urine of pregnant women and mares	Corpus luteum hormone					
16	Progesterone	Of corpus luteum hormone	Corpora lutea of sows				1.0		1.0
17	Testosterone	Androgen	Testes of bulls					0.010	
18	Thyroxine	Essential component of thyroid hormone	Thyroid gland						

* Hippuline is believed to be an isomer of equilin.

STRUCTURAL FORMULAS OF HORMONES

1. Allopregnanediol

2. Allopregnanolone

3. Androsterone

4. Corticosterone

5. Dehydroiso-
   androsterone

6. Dihydroequilenine

7. Epi-allopregnanol-
   3-one-20

8. Epinephrine

9. Equilenine

10. Equilin
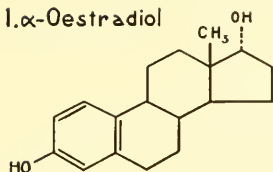
11. α-Oestradiol

12. β-Oestradiol
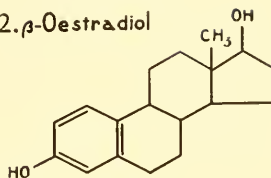
13. Oestriol
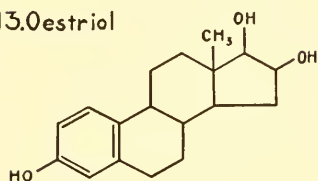
14. Oestrone
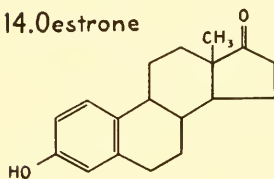
15. Pregnanediol
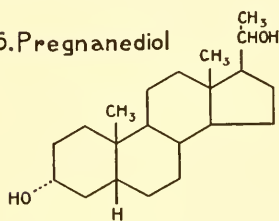
16. Progesterone
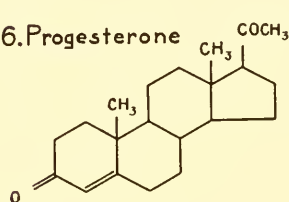
17. Testosterone
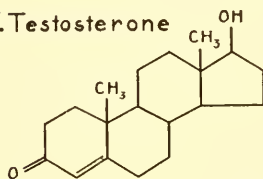
18. Thyroxine
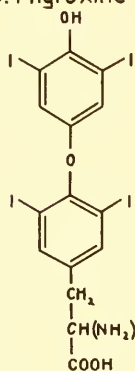
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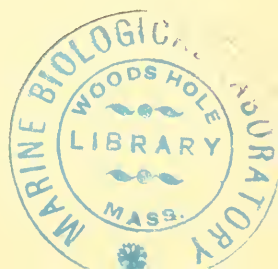
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